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Review Article

Efficacy and Safety of Paclitaxel and Carboplatin for Platinum-Sensitive Ovarian Cancer: A Systematic Review and Meta-Analysis

Yan Zhou [1] **and Wei Guo** [1,2]

[1]*Department of Laboratory Medicine, Zhongshan Hospital, Fudan University, No. 111 Yi Xue Yuan Road, Shanghai 200032, China*
[2]*Department of Laboratory Medicine, Xiamen Branch, Zhongshan Hospital, Fudan University, No. 668 Jin Hu Road, Xiamen 361015, China*

Correspondence should be addressed to Wei Guo; zs-guowei@hotmail.com

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Purpose. Paclitaxel and carboplatin are novel anticancer drugs that have emerged in recent years, while there is still a lack of clinical consensus on these two drugs. The study conducted a meta-analysis and systematic review to analyze the efficacy and safety of paclitaxel and carboplatin for platinum-sensitive ovarian cancer. *Methods.* A systematic search was carried out in three databases of the Cochrane Library, Embase, and PubMed from the inception of each database to March 2021, and defined the progression-free survival and overall survival as the primary outcomes. Data analysis was performed using STATA 15.1. *Results.* Altogether, five randomized controlled trials (RCTs) were included in the meta-analysis, involving 2,740 patients, including 1317 in the CD (carboplatin doxorubicin) group and 1423 in the CP (carboplatin plus paclitaxel) group. It was found that pooled OS demonstrated no significant differences between the CD group and CP group (HR = 1.02, 95% CI = 0.89–1.18, $P = 0.340$), and the differences were not statistically significant in progression-free survival (HR = 0.84, 95% CI = 0.71–0.99, $P = 0.140$), thrombocytopenia (OR = 0.23, 95% CI = 0.09–0.58, $P = 0.775$), and grade II alopecia between the two groups (OR = 9.41, 95% CI = 6.57–13.47, $P = 0.215$). *Conclusion.* Current evidence suggests that paclitaxel and carboplatin do not produce more satisfactory results with respect to overall survival and reduction of side effects in treating platinum-sensitive ovarian cancer, and further studies are needed.

1. Introduction

According to the latest global cancer data analysis, ovarian tumor, a cancer that forms in the ovaries, is one of the most invasive gynecologic malignancies worldwide [1]. A total of 313,959 new cases (1.6%) and 207,252 deaths (2.1%) of ovarian cancer were reported in 2020 worldwide, ranking 8th in the incidence and mortality of female malignancies. Age-standardized incidence and mortality rates for ovarian cancer were 7.1%, 4.1%, and 5.8%, 4.2% (per 100,000 population) in developed and developing countries, respectively [2, 3]. As ovarian cancer is mostly asymptomatic in the early stage and due to the lack of effective screening methods, most patients are found to be already in the middle or late stages of the disease when detected, thereby leading to poor prognosis [4]. Epithelial ovarian cancer is a malignant tumor that is highly sensitive to chemotherapy, which is the main adjuvant treatment for epithelial ovarian cancer [5]. Adjuvant chemotherapy given after initial cytoreductive surgery or staged surgery in patients who are newly diagnosed with epithelial ovarian cancer is an important part of tumor control [6, 7].

Platinum-based combination chemotherapy is recommended by the NCCN guidelines as the first-line chemotherapy regimen for epithelial ovarian cancer [8]. With the same mechanism of action as cisplatin, carboplatin can be used in combination with a variety of anticancer drugs due to no cross-resistance with nonplatinum anticancer drugs

Although cisplatin and carboplatin have similar efficacy, they have different toxic side effects [9]. The neurotoxicity of cisplatin overlaps with the side effects of paclitaxel; therefore, NCCN guidelines recommend carboplatin, which is less toxic and has relatively high drug activity, as the drug of choice for ovarian cancer chemotherapy (NCCN Ovarian Cancer Clinical Practice Guidelines (2019.V3)) [10].

Paclitaxel is a new anticancer drug that has come into use in recent years, which has extensive antitumor effects, mainly by acting on the microtubule system to inhibit cell division, and is considered to be a better chemotherapeutic agent for the clinical treatment of ovarian cancer [11]. Data have been reported from several clinical trials on carboplatin combined with paclitaxel in chemotherapy-sensitive ovarian cancer in recent years, whereas there is a lack of clinical consensus on these two drugs. The present study aims to retrieve current evidence from relevant randomized controlled group studies and systematically evaluate the efficacy and safety of carboplatin combined with paclitaxel in treating epithelial ovarian cancer through a meta-analysis, so as to provide some reference for making clinical decision.

2. Materials and Methods

2.1. Ethics Statement. No ethical approval and patient consent were needed for this meta-analysis as it was conducted based on previously published studies.

2.2. Data Sources and Searches. Two researchers used MeSH terms and free keywords ((paclitaxel[Title]) AND (carboplatin[Title])) AND (platinum-sensitive ovarian cancer[Title]) to independently carry out a systematic search on the Cochrane Library, PubMed, and Embase until March 2021. Only randomized controlled trials (RCTs) published in English were included, with no limitation on the research area. Besides, the reference materials were also identified for further evaluation.

2.3. Study Selection and Quality Assessment. The following were the inclusion criteria for the meta-analysis: (1) the study type was a randomized controlled trial (RCT); (2) patients receiving chemotherapy plus carboplatin and paclitaxel compared with chemotherapy carboplatin alone; (3) patients were clinically diagnosed with platinum-sensitive recurrent ovarian cancer (including the first platinum-sensitive recurrence or the subsequent platinum-sensitive recurrence) on chemotherapy; (4) the outcomes of interest were efficacy and toxicity; (5) only papers with full text were included.

Studies were excluded from the meta-analysis if the patients had other serious illnesses, such as cancer, liver and kidney disease, and cardiovascular disease. Review articles, conference abstracts, non-English articles, case reports, animal studies, and articles without abstract or available full text were excluded.

The risk of bias in each included RCT was estimated by employing the Cochrane risk of bias tool, which covers the following aspects: blinding of participants and personnel, random sequence generation, allocation concealment, blinding of outcome assessment, selective outcome reporting, incomplete outcome data, and other sources of bias. Also, the risk of bias for each field was graded as low, high, or unclear [12].

2.4. Data Extraction. The information from each trial was extracted independently by two researchers, mainly including publication year, lead author, patient number, treatment regimen, and outcome measures. In case of any discrepancy, two researchers resolved it by discussion or consulted a third investigator.

2.5. Statistical Analysis. The STATA 15.1 software was adopted for statistical analysis. Chi-square and the I^2 statistic were used to assess the significance and the degree of heterogeneity across studies, respectively. Significant heterogeneity was suggested when I^2 value was larger than 50%, and then the random-effects model was adopted; otherwise, we employed a fixed-effects model, with a P value <0.05 regarded to indicate a statistically significant difference.

3. Results

3.1. Literature Review and Research Characteristics. The preliminary search identified a total of 1,438 papers, 1402 of which were excluded after careful review of the full text, titles and abstracts. Meanwhile, a total of 36 studies were used to carry out the potential relevance, and 31 of them were excluded after referring to the full text (14 without detailed data on patient treatment response or clinical characteristics, 13 assigned to the control group, 3 lacking sufficient data, and 1 that was reviewed). Finally, in this meta-analysis, 5 trials [13–17] including 2740 patients met the inclusion criteria. Figure 1 shows the exclusion reasons.

A brief description of the characteristics of eligible studies is presented in Table 1. There are 2,740 patients enrolled in the five included trials, ranging from 24 to 89 years in age, with 1,317 patients receiving carboplatin-pegylated liposomal doxorubicin therapy (CD therapy) and 1,423 patients receiving carboplatin-paclitaxel treatment (CP therapy). No significant differences were found in the clinical data between the treatment and control groups ($P > 0.05$). The clinical information of the included trials is summarized in detail in Table 1.

3.2. Outcomes and Synthesized Results

3.2.1. Pooled Analysis of Overall Survival (OS) Comparing CD with CP. No significant difference was demonstrated by the pooled OS between the CD group and CP group (HR = 1.02, 95% CI = 0.89–1.18, $P = 0.340$). Also, subgroup analysis revealed U Wagner (HR = 0.99, 95% CI = 0.85–1.16, $P = 0.94$) and Sven Mahner group (HR = 1.18, 95% CI = 0.85–1.63, $P = 0.33$). The results are shown in Figure 2.

3.2.2. Pooled Analysis of Progression-Free Survival (PFS) Comparing CD with CP was Performed. No statistically

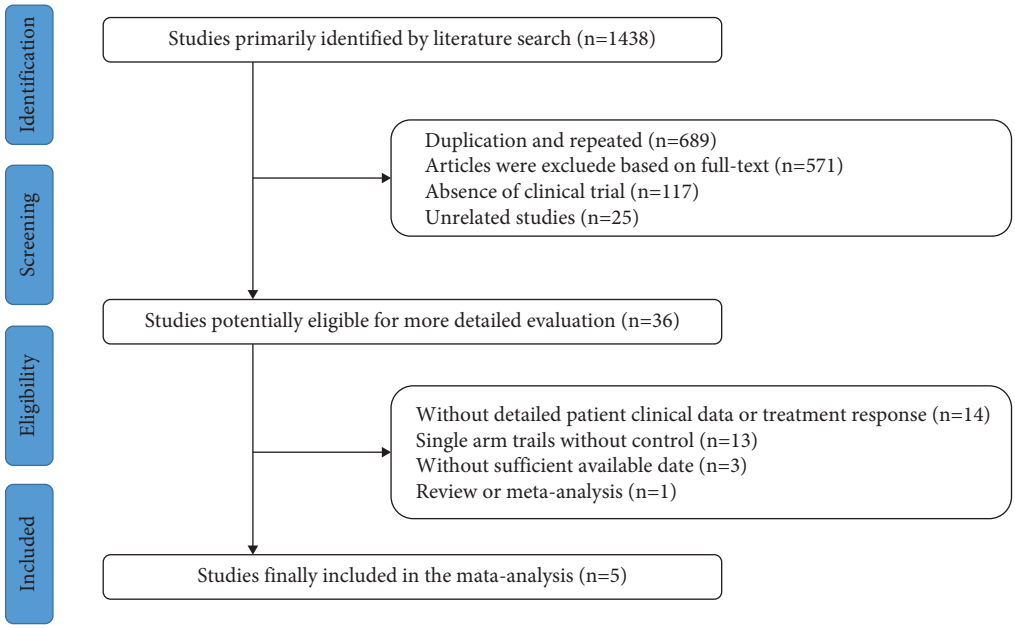

Figure 1: Articles retrieved and assessed for eligibility.

Table 1: Brief description of included studies.

Study year	Treatment regimen		Age (mean, range)	
	CD	CP	CD	CP
L. Gladieff, 2012	161	183	60.0 (24~82)	60.0 (30~80)
U Wagner, 2012	466	509	60.5 (24~82)	61.0 (27~82)
Dimitrios Bafaloukos, 2010	93	96	63.0 (37~81)	62.0 (38~89)
Eric Pujade-Lauraine, 2010	466	507	60.5 (24~82)	61.0 (27~82)
Sven Mahner, 2014	131	128	60.0 (30~80)	63.0 (27~82)

CD: carboplatin-pegylated liposomal doxorubicin; CP: carboplatin-paclitaxel.

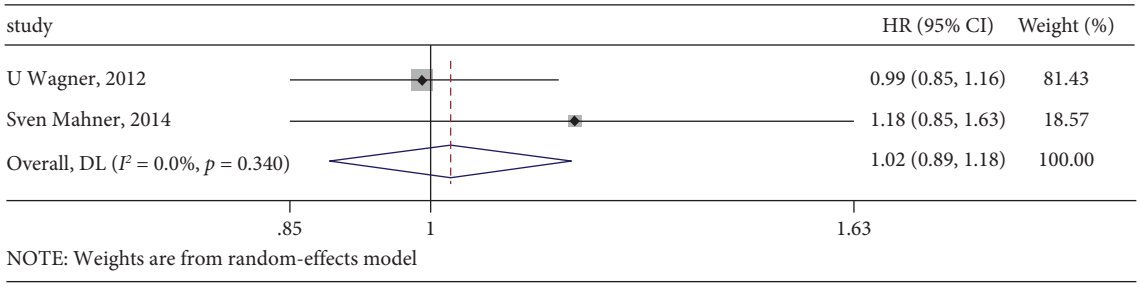

Figure 2: Pooled analysis of overall survival (OS).

significant difference in PFS was shown by the pooled estimates of effect sizes (HR = 0.84, 95% CI = 0.71–0.99, $P = 0.140$). Moreover, subgroup analysis revealed L. Gladieff (HR = 0.73, 95% CI = 0.58–0.90, $P = 0.004$), Eric Pujade-Lauraine (HR = 0.82, 95% CI = 0.72–0.94, $P = 0.005$), and Sven Mahner (HR = 1.05, 95% CI = 0.79–1.40, $P = 0.73$). The results are shown in Figure 3.

3.3. Toxicity and Side Effects. The most common adverse reactions observed during the treatment were Grade II alopecia, Grade III-IV neutropenia, Grade III neurotoxicity, thrombocytopenia, mucositis, hand-foot syndrome, as well as nausea. Chills, rashes, fever, and headaches are not common although they have also been reported. None had severe diarrhea, shock, liver dysfunction, or renal insufficiency. Besides, the difference was shown to be statistically significant in the incidence of myelosuppression between the two groups.

3.3.1. Pooled Analysis of Grade 3 and 4 Neutropenia Comparing CD with CP. No significant difference was shown by pooled estimates of effect sizes in grade 3 and 4 neutropenia (OR = 1.47, 95% CI = 1.08–2.01, $P = 0.102$). Also, subgroup analysis revealed L. Gladieff (OR = 1.93, 95% CI = 1.26–2.93, $P = 0.015$), Dimitrios Bafaloukos (OR = 0.79, 95% CI = 0.43–1.45, $P > 0.05$), Eric Pujade-Lauraine (OR = 1.46,

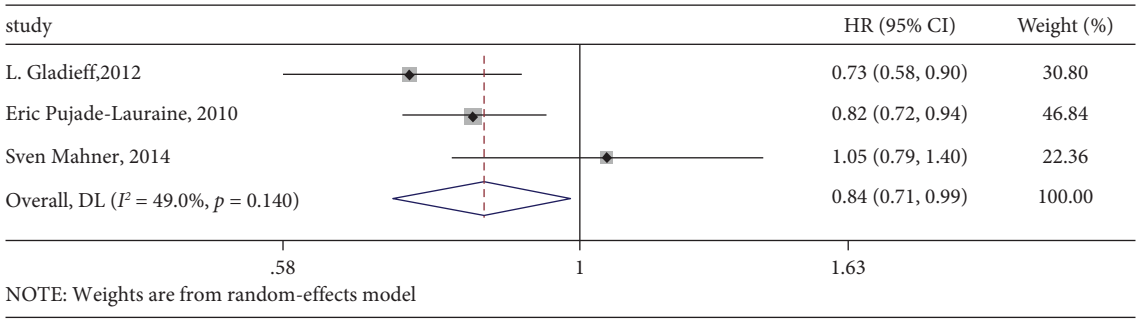

Figure 3: Pooled analysis of progression-free survival (PFS).

95% CI = 1.11–1.91, $P < 0.001$), and Sven Mahner (OR = 1.81, 95% CI = 1.07–3.04, $P = 0.025$). The results are presented in Figure 4.

3.3.2. Pooled Analysis of Grade II Alopecia Comparing CD with CP. Pooled estimates of effect sizes indicated no significant difference in grade II alopecia (OR = 9.41, 95% CI = 6.57–13.47, $P = 0.215$). Also, subgroup analysis revealed L. Gladieff (OR = 9.38, 95% CI = 5.31–16.59, $P < 0.001$), Dimitrios Bafaloukos (OR = 3.68, 95% CI = 1.32–10.27, $P = 0.003$), Eric Pujade-Lauraine (OR = 11.82, 95% CI = 8.11–17.21, $P < 0.001$), and Sven Mahner (OR = 9.64, 95% CI = 5.07–18.33, $P < 0.001$). The results are shown in Figure 5.

3.3.3. Pooled Analysis of Thrombocytopenia Comparing CD with CP. There was no significant difference in thrombocytopenia, as suggested by pooled estimates of effect sizes (OR = 0.23, 95% CI = 0.09–0.58, $P = 0.775$). Also, subgroup analysis indicated Dimitrios Bafaloukos (OR = 0.19, 95% CI = 0.084–0.91, $P = 0.016$) and Sven Mahner (OR = 0.26, 95% CI = 0.08–0.79, $P = 0.007$). The results are shown in Figure 6.

3.3.4. Pooled Analysis of Grade III Neurotoxicity Comparing CD with CP. There was no significant difference in Grade III neurotoxicity, as shown by the pooled estimates of effect sizes (OR = 4.90, 95% CI = 2.77–8.66, $P = 0.331$). Also, subgroup analysis revealed Dimitrios Bafaloukos (OR = 14.53, 95% CI = 0.82–258.08, $P = 0.029$), Eric Pujade-Lauraine (OR = 5.47, 95% CI = 3.45–8.65, $P < 0.001$), and Sven Mahner (OR = 2.05, 95% CI = 0.50–8.36, $P = 0.27$). The results are displayed in Figure 7.

3.3.5. Pooled Analysis of Mucositis and Hand-Foot Syndrome Comparing CD with CP. Pooled estimates of effect sizes demonstrated significant differences in mucositis and hand-foot syndrome (OR = 0.22, 95% CI = 0.09–0.53, $P = 0.002$). In addition, subgroup analysis revealed Dimitrios Bafaloukos (OR = 0.11, 95% CI = 0.05–0.24, $P < 0.001$), Eric Pujade-Lauraine (OR = 0.51, 95% CI = 0.33–0.78, $P < 0.001$), Eric Pujade-Lauraine (OR = 0.18, 95% CI = 0.09–0.35, $P < 0.001$), and Sven Mahner (OR = 0.15, 95% CI = 0.01–2.86, $P = 0.089$), as shown in Figure 8.

3.3.6. Pooled Analysis of Nausea Comparing CD with CP. The difference in nausea between the two groups was not significant, as revealed by the pooled estimates of effect sizes (OR = 0.79, 95% CI = 0.43–1.45, $P = 0.232$). Also, subgroup analysis revealed Eric Pujade-Lauraine (OR = 0.69, 95% CI = 0.53–0.90, $P < 0.001$) and Sven Mahner (OR = 1.54, 95% CI = 0.42–5.57, $P = 0.47$), as shown in Figure 9.

3.4. Assessment of Quality and Bias. Based on the results of the Cochrane Collaboration Bias Risk Tool, shared studies have an ambiguous risk of bias. The randomization method was clearly described and appropriate in 5 studies [13, 14]. The bias of each study is shown in Figure 10, and the bias summary is shown in Figure 11.

4. Discussion

Ovarian cancer is the main cause of death from gynecologic tumors [18, 19] as well as the fifth leading cause of cancer death in women [20]. Due to the anatomical characteristics of ovarian cancer, there are no specific symptoms in its early stage and a lack of sensitive and specific early screening methods [21], resulting in 70% of patients being diagnosed at an advanced stage [22, 23]. The 5-year survival rate of patients with early-stage ovarian cancer has been further improved in recent years with advances in medical technology, but for patients with advanced and recurrent disease [24], the available treatments are still unsatisfactory. Therefore, the selection of chemotherapy regimen is crucial. The classification of recurrent ovarian cancer is based on the time between recurrence and the last chemotherapy, according to the NCCN guidelines for the diagnosis and treatment of ovarian cancer [25]. Patients are considered platinum-sensitive if they recur 6 months or more after initial chemotherapy. Patients with recurrence 6 months or more after initial chemotherapy are regarded to have platinum-sensitive recurrence, and platinum-containing combination regimens are recommended for second-line chemotherapy [26]. Patients are considered to have platinum-resistant relapses if they relapse within 6 months after the completing the initial chemotherapy. Non-platinum-based chemotherapy regimens are recommended for those who recur within 6 months of the first chemotherapy [27].

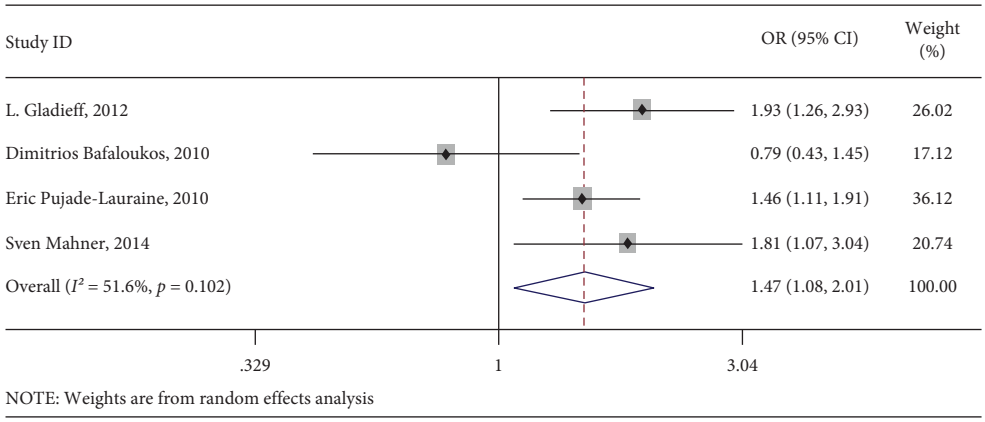

Figure 4: Pooled analysis of grade 3 and 4 neutropenia.

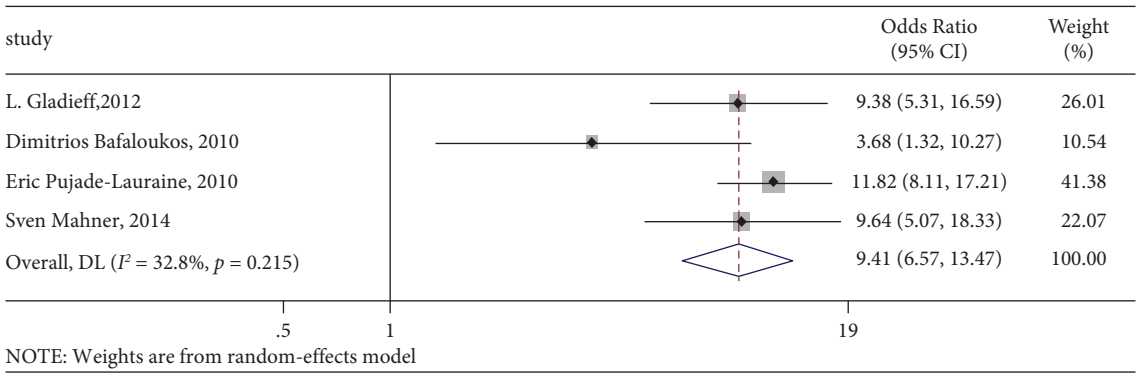

Figure 5: Pooled analysis of grade II alopecia.

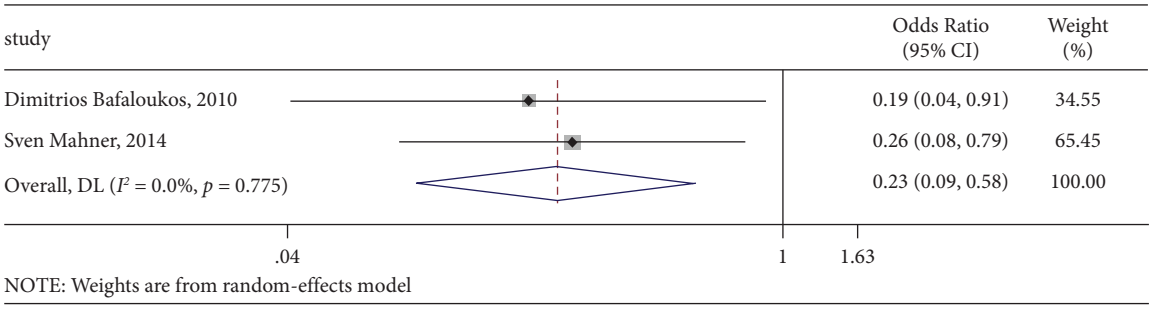

Figure 6: Pooled analysis of thrombocytopenia.

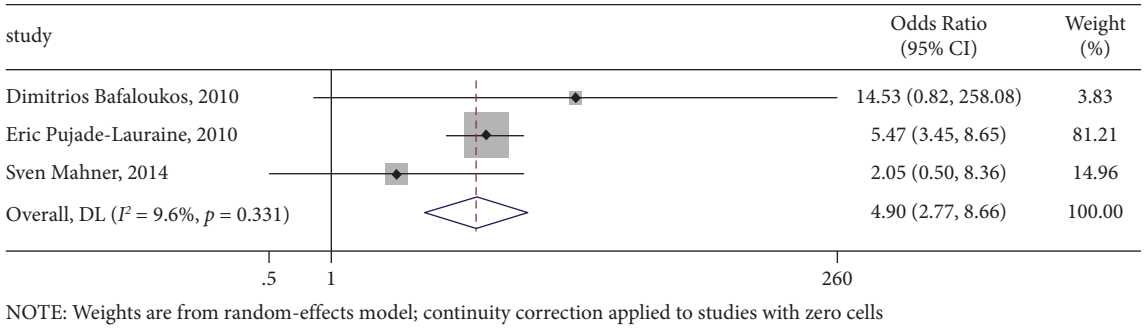

Figure 7: Pooled analysis of grade III neurotoxicity.

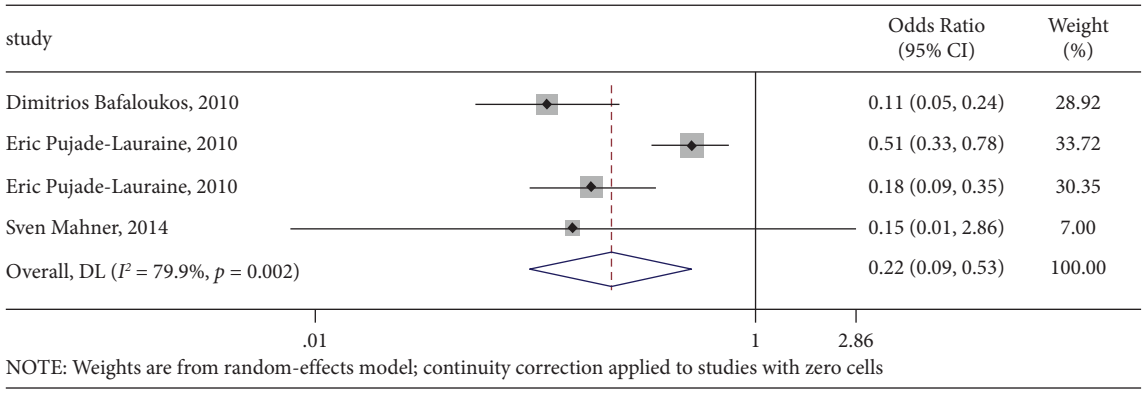

Figure 8: Pooled analysis of mucositis and hand-foot syndrome.

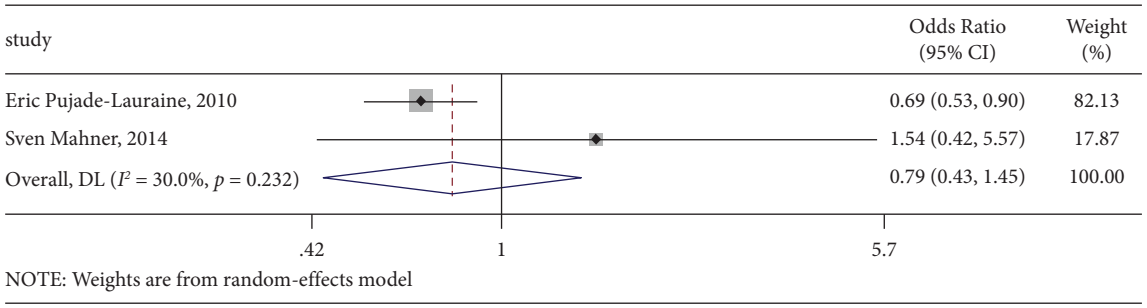

Figure 9: Pooled analysis of nausea.

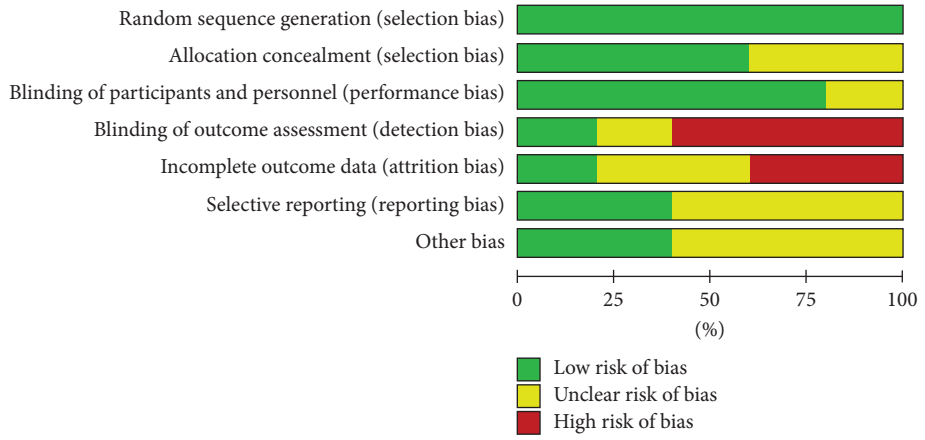

Figure 10: The risk of bias in studies (A) assessment.

Paclitaxel is a cell cycle specific cytotoxic drug, which blocks cell mitosis and induces apoptosis through pro-microtubule protein polymerization, and exerts anti-tumor effects [28]. Paclitaxel was approved to be used to treat metastatic ovarian cancer after failure of first-line or sequential chemotherapy by the US FDA in 1992, and began to be applied as a first-line chemotherapy agent for ovarian cancer in 1996 [29]. Nevertheless, since paclitaxel is derived from yew bark, it is necessary to add surfactant polyoxyethylene castor oil-anhydrous ethanol in the injection to increase its water solubility, and polyoxyethylene castor oil has biological activity, which can cause various toxic side effects, such as allergy, toxic kidney injury, neurotoxicity, and cardiovascular toxicity [30]. A phase II clinical trial conducted by Teneriello et al. [31] demonstrated the effectiveness of albumin-conjugated paclitaxel in treating platinum-sensitive recurrent ovarian cancer (37 cases), peritoneal cancer (9 cases), and fallopian tube cancer (1 case), with an objective response rate of 64% (CR 31.8%; PR 31.8%) and a PFS of 8.5 months. In another small sample size study which wascompared with the solvent-basedpaclitaxel group, lesion reduction was used as the evaluation index of short-term efficacy. There was a significantly higher CR rate detected in the albumin-bound paclitaxel group (60% vs 18.8%, $P < 0.05$). Nevertheless, the difference in objective response rate was not significant between the two groups (90% vs 75%). Analysis of PFS in platinum-sensitive relapse patients yielded a median PFS

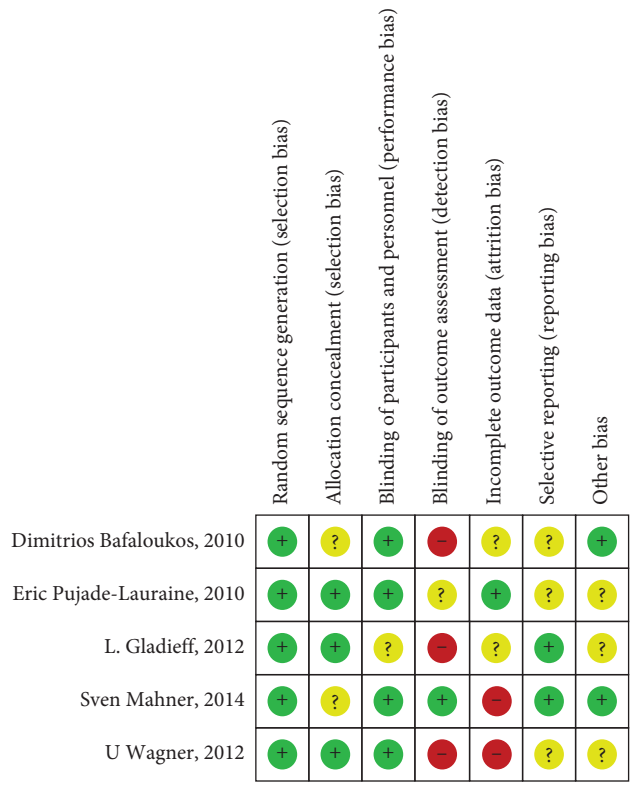

Figure 11: The risk of bias in studies (B) summary.

of 10.25 months in the albumin-bound paclitaxel group and 7.5 months in the solvent-based paclitaxel group, respectively, and the difference was significant. In our study, the existing clinical evidenceshows that carboplatin combined with paclitaxelin the treatmentof ovarian cancer are equally effective and relatively safe compared to the carboplatin-pegylatedliposomal doxorubicin therapy. Therefore, paclitaxel andcarboplatin can be a novel, safe and effective way to treat ovarian cancer.

4.1. Limitations. This study also has some limitations. First of all, some negative results should not have been published and excluded, which would produce publication bias. The failure in the details of the design method would also be a possible source of increased heterogeneity in the included studies.

Secondly, the RCTs included were generally of poor quality since most of the risk items were unclear, especially the allocation of occultation, blindness, as well as selective outcome reports, which may reduce the credibility of our conclusions. Therefore, it is recommended that future researchers should follow the CONSORT reporting specification. Regarding the implementation of blind methods, due to the subjective symptom scores reported as results in this study, third-party evaluators may adopt blind methods to reduce bias and improve the reliability of results. Also, the number of studies included was so small that there was a lack of a large sample size for high-quality studies.

5. Conclusion

As we know, the present systematic review and meta-analysis is the first to evaluate the efficiency of paclitaxel and carboplatin in treating platinum-sensitive ovarian cancer, with a total of 5 papers involving 2740 cases included. The meta-analysis results showed the efficiency of treating platinum-sensitive ovarian cancer, and the paclitaxel and carboplatin in the treatment of platinum-sensitive ovarian cancer significantly improved overall survival and reduced toxicity. However, this result needs to be further verified by high-quality studies with large samples.

Data Availability

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

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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