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Comparison of pegylated liposomal doxorubicin and paclitaxel plus carboplatin-based chemotherapy as first line treatment for patients with ovarian cancer: a systematic review and meta-analysis of randomized controlled trials

S.-Q. SHI[1], F.-F. JIANG[1], T. HONG[1], Y. ZHUANG[1], L. CHEN[1], X.-L. HUANG[2]

[1]Department of Gynecology and Obstetrics, the Fifth Affiliated Hospital of Sun Yat-sen University
[2]Department of Respiratory Medicine, the Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, Guangdong, P.R. China

Shaoquan Shi and *Fangfang Jiang* contributed equally to this work

Abstract. – We reviewed studies comparing survival outcomes such as overall survival (OS), progression free survival (PFS), and toxicity profile between patients treated with Pegylated Liposomal Doxorubicin (PLD) combination and those treated with paclitaxel combination for ovarian cancer. We conducted systematic searches in various databases including Medline, Cochrane Controlled Register of Trials (CENTRAL), ScienceDirect, and Google Scholar from inception until August 2019. We used the Cochrane risk of bias tool to assess the quality of published trials. We carried out a meta-analysis with random-effects model and reported pooled Hazard ratios (HR) or Risk ratios (RR) with 95% confidence intervals (CIs). In total, we analysed 7 studies including 3,676 participants. All the studies were randomized controlled trials, while majority of studies had low bias risks. We did not find significant evidence for any of these outcomes except progression free survival (favoured PLD combination therapy pooled HR=0.87; 95% CI: 0.77-0.98). Worst grade toxicities like allergy (pooled RR: 1.86; 95% CI: 1.06-3.24) and neurotoxicity (pooled RR: 5.59; 95% CI: 1.43-21.84) were significantly higher among patients receiving paclitaxel combination therapy when compared to patients receiving PLD combination therapy. To summarize, PLD combination therapy is non-inferior to paclitaxel combination therapy in the management of ovarian cancer with respect to survival outcomes and worst grade toxicity profile. However, clinical recommendations cannot be made, as the evidence is not conclusive or significant enough.

Key Words:
Carboplatin, Doxorubicin, Meta-Analysis, Ovarian Cancer, Paclitaxel.

Introduction

Ovarian cancer is one of the leading causes of mortality among the gynaecological tumours[1]. GLOBOCAN 2018 has reported that about 295,000 new cases and 185,000 deaths occurred due to ovarian cancer[1]. More than half of these cases and deaths occur in developing regions like Asia[1]. It usually has an asymptomatic onset and unobtrusive progression of disease. Even if symptomatic, non-specific symptoms such as pain, abdomen swelling, weight loss, and change in bowel and bladder habits occur[2]. This leads to delay in diagnosis and most of the women with ovarian cancer are found in stage III or IV of disease. This makes ovarian cancer to have one of the worst prognoses (ranging from 37% to 54% in European and American region) among the gynecological tumours[3,4].

The standard approach for treatment of ovarian cancer patients is dependent on the grade of disease. Women with low grade stage I cancer may not require chemotherapy while high grade cases require a combination chemotherapy[2]. Previous evidence and experiences have established that the platinum agents such as carboplatin and

Corresponding Author: Shaoquan Shi, MD; e-mail: shisq2001@sohu.com

cisplatin, are as the most biologically active cytotoxic agents in the management of ovarian cancer. Out of these two, carboplatin is more preferred as it has lesser toxicity and an equivalent efficacy[5]. Carboplatin is commonly provided in combination with paclitaxel. However, there has been an increasing report of cumulative toxicities which includes residual neurotoxicity following first line treatment. Hence, many investigators nowadays are seeking newer therapeutic combinations in treating ovarian cancer[6].

Pegylated liposomal doxorubicin (PLD), an anthracycline anticancer drug, in combination with carboplatin has been found to be efficacious in patients with platinum sensitive ovarian cancer[7]. Anthracyclines interacts with the deoxyribonucleic acid (DNA) and affects the functions of cell that relies on DNA. It also interacts and alters the functions of cell membranes leading to generation of hydroxyl radicals and hydrogen peroxide that are destructive to cells[8]. Pegylated coating of PLD forms a hydrophilic barrier protecting the liposomes from reticuloendothelial system detection and makes the drug active for a longer period of time[9,10]. PLD does not enter into tight capillary junctions like gastrointestinal tract and heart because of the size of liposomes[11]. This makes the PLD carboplatin combination to have better safety profile when compared to other non-doxorubicin combination chemotherapeutic agents like paclitaxel and carboplatin. Ironically, there have been no systematic efforts to synthesize the outcomes between these two different combination medications. This meta-analysis is therefore being planned with the aim to compare PLD plus carboplatin and paclitaxel plus carboplatin in the management of ovarian cancer patients.

Materials and Methods

Type of Studies to be Included

We included parallel arm individual randomized, quasi randomized or cluster randomized controlled trials for the current review. Studies reported as full text will be included while studies published with only abstract or unpublished data were excluded.

Type of Participants

We included studies conducted among patients with ovarian cancer irrespective of the stage of tumour.

Type of Intervention

We included studies that directly compared the effectiveness of PLD plus carboplatin and paclitaxel plus carboplatin for the treatment of ovarian cancer.

Type of Outcome Measure

Following outcomes measures were seen in our review: overall survival (OS), progression free survival (PFS), disease progression rate (PD), overall response rate (ORR; complete response and partial response), disease control rate (DCR), toxicity profile (worst grade of toxicity grade $\geq$ 3: hematological conditions such as anemia, leukopenia, thrombocytopenia, neutropenia; non-hematological conditions like fatigue, allergy, nausea or vomiting, cardiac or neurological toxicities). We included the studies reporting any of the outcomes mentioned above in both arms.

Search Strategy

We conducted extensive search in the following databases: Medline (PubMed), Google Scholar, ScienceDirect, Cochrane central register of controlled trials. In addition, search was conducted in the following clinical trial registries: ClinicalTrials.gov, and World Health Organization International Clinical Trials Registry Platform. We searched with a combination of medical subject heading (MeSH) and free text terms including "Paclitaxel plus Carboplatin", "Doxorubicin plus Carboplatin" "Ovarian Tumour", "Overall Survival", "Progression Free Survival", "Ovarian Cancer", "Pegylated Liposomal Doxorubicin" and "Randomized Controlled Trial" in all search engines for the above-mentioned databases. We retrieved all English publications from databases inception to August 2019.

Searching Other Resources

We hand searched the list of references in primary trials which were obtained through our electronic search. We included relevant articles for our review and further analysis. We contacted the authors of the published trials in cases requiring clarification or additional information.

Data Collection and Analysis

Selection of Studies

Two independent investigators performed the literature search independently and did the screening of titles, abstracts, and keywords of the retrieved citations and assessed for the possibility

of inclusion in our review. We obtained full text of the relevant studies. Further screening of abstracts and full text articles were done by the primary and secondary investigators independently and selected the studies satisfying the inclusion criteria of our review. Any disagreements between the investigators during the entire process of selection were resolved either by consensus or after consultation with another investigator. The third investigator monitored the overall quality of the review process. We used the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) check list for reporting our review[12].

Data extraction and management

The primary investigator extracted the required study characteristics for our review from the included studies. The information extracted included general information such as date of extraction, study title, and authors; methods such as study design, participants, and study setting; participant's characteristics such as total number of participants in each arm, baseline and endline outcome measures, and inclusion and exclusion criteria; interventions characteristics such as intervention and comparison group details and follow up duration; outcomes section such as primary, secondary outcomes, time taken for outcome assessment, and other details necessary for assessing the risk of bias of included studies.

Primary and secondary investigators performed data extraction related to outcome measures from the studies included in our review. The primary investigator transferred the obtained data into the statistical software RevMan (version 5.3 Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The third investigator double checked data entries for correctness by comparing it to the data in the study reports.

Risk of Bias Assessment in Included Studies

Two independent investigators assessed the risk of bias for included RCTs using the Cochrane risk of bias tool[13]. Following domains were assessed: random sequence generation, allocation concealment, blinding of outcome assessment and study participants, incomplete outcome data, selective reporting of outcome and other sources of bias. For each of the mentioned domains above, we graded the risk of bias as low (if adequate information was provided), as high (if the information was inadequate or not performed), or as unclear (if the information was missing).

Statistical Analysis

Meta-analysis was performed using the software RevMan 5.3 (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For time-to-event outcome data such as overall survival and progression free survival, pooled estimate can be calculated using log of hazard ratio (ln{HR}) and standard error of ln(HR)[14]. First, hazard ratio (HR) with 95% Confidence interval (CI) was retrieved from the trials. Logarithmic value of HR was calculated for each of the HR estimate. Standard error of ln(HR) was calculated using the following equations:

first, variance of logarithmic HR was calculated using upper and lower confidence limits of HR and cumulative distribution function of the normal distribution.

$$\text{Variance } (\ln\{HR\}) = [\ln(\text{upper CI of HR}) - \ln(\text{lower CI of HR})/2\times 1.96]$$

Standard error of logarithmic HR was calculated by taking the square root of variance of logarithmic HR.

$$\text{Standard error } (\ln\{HR\}) = \sqrt{\text{Variance } (\ln\{HR\})}$$

Logarithmic HR and its standard error were then entered into the RevMan software 5.3 (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) to estimate the pooled effect in terms of Hazard Ratio.

For dichotomous outcomes such as ORR, PD, DCR, and toxicity profile, we obtained the numbers of events and of participants in each group and entered those into the RevMan software 5.3 (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) to estimate the pooled effect size in terms of Relative Risk.

We performed appropriate analyses based on the level at which the randomization was performed (either individual or clustered). We found no cluster randomized trials satisfying the eligibility criteria and did not require appropriate clustering adjustments. We used a random effects model with inverse variance[15]. In case of missing data, we contacted authors of the trials, and if still not able to retrieve the necessary data, we followed an imputation method.

Assessment of Heterogeneity

We applied Chi-square tests of heterogeneity to assess between-study variance and I^2 statistics to quantify inconsistencies[13]. We classified heterogeneity according to I^2 as mild (I^2 <25%) moderate (I^2 between 25 and 75%) or substantial (I^2 >75%). Forest plot was used to graphically represent both pooled and study specific estimates. We did not perform meta-regression as the outcomes did not have the required number of studies to perform meta-regression (minimum of 10 studies).

Assessment of Reporting Biases

We assessed reporting biases by checking whether the included trials or studies are registered in a trial registry and whether their full protocols are available. If available, we compared the list of outcomes in the protocol with the list of outcomes mentioned in the full published trial. We did not assess for publication bias as the outcomes did not have the required number of studies to assess the publication bias (minimum of 10 studies).

Results

Study Selection

We conducted a systematic search to find studies that directly compared the effectiveness of PLD plus carboplatin and paclitaxel plus carboplatin for the management of ovarian cancer from the dates of database inception until August 2019. We identified a total of 905 citations, 322 studies from Medline, 153 from CENTRAL, 299 from ScienceDirect, 112 from Google Scholar, 14 from ClinicalTrials.gov, and 5 from WHO ICTRP (Figure 1). After the first screening stage (title, abstract, and keywords), we retrieved 27 relevant studies. We reviewed their full texts for eligibility criteria. At the same, we reviewed the bibliographies of the retrieved articles and found three more relevant studies. Finally, we analysed data from 7 studies with 3,676 participants satisfying the inclusion criteria[7,16-21].

Characteristics of the Studies Included

Table I lists the characteristics of the studies analysed. All the included studies were RCTs.

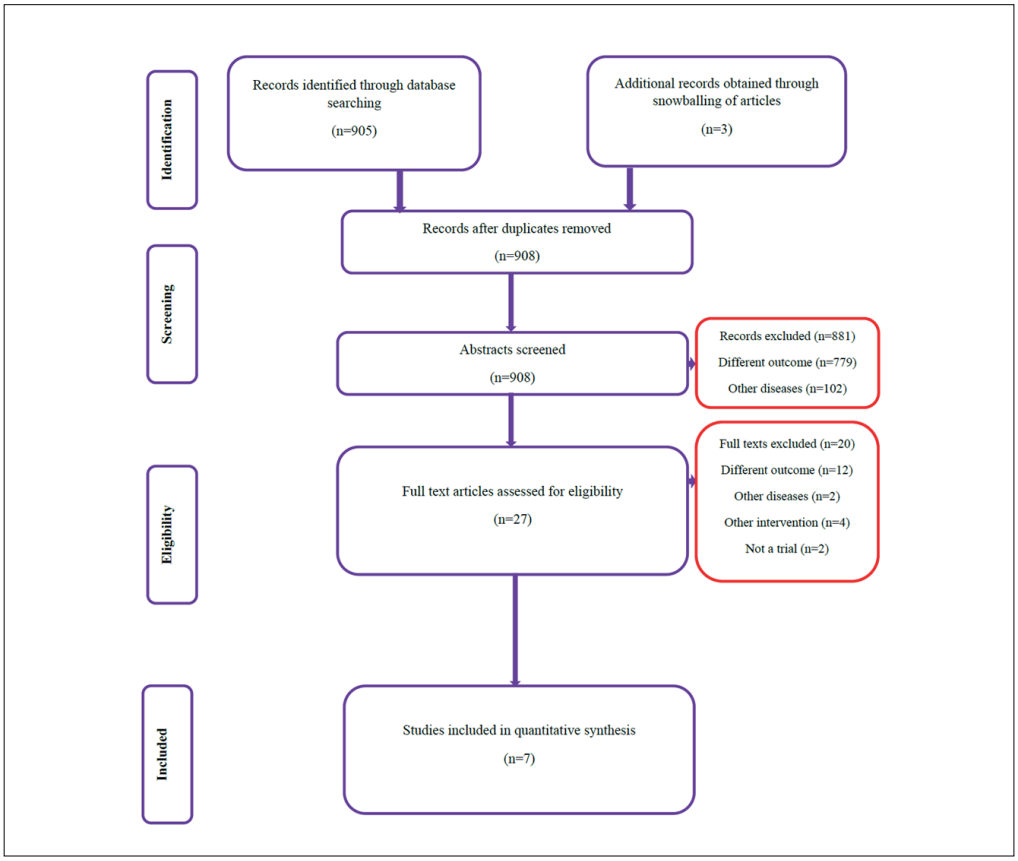

Figure 1. PRISMA flow chart showing the selection of studies for the current review (n=7).

Table I. Characteristics of the included studies, N = 7.

S. No	Author and year	Country	Study design	Sample size in PLD combination arm	Sample size in the Paclitaxel combination arm	Interventions	Follow up	Median age of the study participants in PLD combination arm	Median age of the study participants in Paclitaxel combination arm
1.	Bafaloukos 2010[16]	Greece	Randomized controlled trial	93	96	**PLD combination:** Carboplatin AUC5 + pegylated LD 45 mg/m^2, d1q28). **Paclitaxel combination:** Six cycles of CP (carboplatin AUC5 + paclitaxel 175 mg/m^2, d1q21)	Median follow-up 43.6 months	Not given separately (median age of total participants=63 years)	
2.	Gladieff 201217	16 countries from Europe Middle East, Australia, North America and New Zealand	Multi-national randomized controlled trial	161	180	**PLD combination:** Carboplatin (C) AUC 5 plus PLD 30 mg/m^2 on day 1 every 4 weeks. **Paclitaxel combination:** C AUC 5 plus paclitaxel (P) 175 mg/m^2 on day 1 every 3 weeks	Follow-up for toxicity was done prior to each cycle and tumour assessments every 3 months while patients were on treatment. Follow-up after treatment discontinuation every 3 months for 2 years and every 6 months thereafter for 5 year	60 years	60 years
3.	Kurtz 2011[18]	16 countries	Multi-national randomized controlled trial	71	86	**PLD combination:** Carboplatin (C) AUC 5 plus PLD 30 mg/m^2 on day 1 every 4 weeks **Paclitaxel combination:** C AUC 5 plus paclitaxel (P) 175 mg/m^2 on day 1 every 3 weeks.	Follow-up at 3,6,9 and 12 months	74 years	73 years

Table continued

Table I *(Continued)*. Characteristics of the included studies, N = 7.

S. No	Author and year	Country	Study design	Sample size in PLD combination arm	Sample size in the Paclitaxel combination arm	Interventions	Follow up	Median age of the study participants in PLD combination arm	Median age of the study participants in Paclitaxel combination arm
4.	Mahner 2014[19]	16 countries	Multi-national randomized controlled trial	131	128	**PLD combination:** Carboplatin (C) AUC 5 plus PLD 30 mg/m^2 on day 1 every 4 weeks **Paclitaxel combination:** C AUC 5 plus paclitaxel (P) 175 mg/m^2 on day 1 every 3 weeks	Follow-up for toxicity was done prior to each cycle and tumour assessments every 3 months while patients were on treatment. Follow-up after treatment discontinuation every 3 months for 2 years and every 6 months thereafter for 5 year	60 years	63 years
5.	Pignata 2011[20]	Italy	Multi-centre randomized controlled Trial	396	407	**PLD combination:** Carboplatin Area under the curve (AUC) 5 plus PLD 30 mg/m^2, **Paclitaxel combination:** Carboplatin AUC 5 plus paclitaxel 175 mg/m^2 every 3 weeks for six cycles.	Median follow-up 40 months	57 years	57 years

Table continued

Table I ***(Continued).*** Characteristics of the included studies, N = 7.

S. No	Author and year	Country	Study design	Sample size in PLD combination arm	Sample size in the Paclitaxel combination arm	Interventions	Follow up	Median age of the study participants in PLD combination arm	Median age of the study participants in Paclitaxel combination arm
6.	Pujade-, Lauraine 2010[7]	16 countries	Multi-national randomized controlled trial	466 :	501	**PLD combination** Carboplatin (C) AUC 5 plus PLD 30 mg/m^2 on day 1 every 4 weeks **Paclitaxel combination:** C AUC 5 plus paclitaxel (P) 175 mg/m^2 on day 1 every 3 weeks.	Follow-up for toxicity was done prior to each cycle and tumour assessments every 3 months while patients were on treatment. Follow-up after treatment discontinuation every 3 months for 2 years and every 6 months thereafter for 5 year	60.5 years	61 years
7.	Wagner 2012[21]	16 countries	Multi-national randomized controlled trial	467	509	**PLD combination:** Carboplatin (C) AUC 5 plus PLD 30 mg/m^2 on day 1 every 4 weeks **Paclitaxel combination:** C AUC 5 plus paclitaxel (P) 175 mg/m^2 on day 1 every 3 weeks.	Follow-up for toxicity was done prior to each cycle and tumour assessments every 3 months while patients were on treatment. Follow-up after treatment discontinuation every 3 months for 2 years and every 6 months thereafter for 5 year	60.5 years	61 years

Except two studies (Greece and Italy)[16,20], all other trials are part of multi-national centrally randomized open label RCT conducted in 16 countries across North America, Europe, Middle East, Australia, and New Zealand[7,17-19,21]. The mean age of study participants ranged from 57 to 74 years in the PLD combination arm, and that in the paclitaxel combination arm ranged from 57 to 73 years. Of the 3,676 participants 1,775 completed the PLD arm and 1,901 the paclitaxel arm. The sample sizes in the studies (both arms together) varied from 157 to 975, while sample size in the PLD arm varied from 71 to 466 patients and in the paclitaxel arm from 86 to 509. Among the 7 studies included, 6 reported on toxicity profile (anemia, neutropenia, thrombocytopenia, allergy, neurotoxicity) 5 reported on nausea and vomiting and fatigue, 4 reported on overall survival, progression free survival, overall response rate, cardiotoxicity and 3 reported on leukopenia, partial and complete response rate.

Methodological Quality of the Studies Included

We performed assessments of risk of bias for RCTs and reported in Table II. All the trials had low risk of bias in relation to random sequence generation and allocation concealment. All the trials had high risk of bias related to blinding of participants and outcome assessment. Intention to treat analysis was performed in all the trials to account for incomplete outcome data. The trials conducted as part of multi-country had high risk of bias related to selective reporting of outcome[7,17-19,21].

Overall Survival (OS)

Among the studies included, four reported on overall survival of ovarian cancer patients following chemotherapy in both arms (PLD + Carboplatin and Paclitaxel + Carboplatin)[16,19-21]. None of the included studies revealed conclusive evidence on the superiority of the drugs in improving overall survival. The pooled HR was 0.98 indicating that PLD combination has lesser death events when compared to Paclitaxel combination (Figure 2). However, the confidence of this pooled estimate crossed the null value (95% CI, 0.87-1.11), and the result is not statistically significant. This shows that PLD combination is non-inferior to paclitaxel combination in terms of overall survival of ovarian cancer patients. Moreover, we found no heterogeneity among the studies reporting response rate with I^2=0%. The Chi-square for heterogeneity also showed absence of significant heterogeneity among the studies reporting overall survival (p=0.53).

Progression Free Survival (PFS)

Five studies reported on progression free survival of ovarian cancer patients following chemotherapy in both arms[7,17-20]. The pooled HR was 0.87 (95% CI: 0.77-0.98) (Figure 3). This indicates that the ovarian cancer patients receiving PLD combination drugs can survive for a longer duration without disease progression when compared to patients receiving paclitaxel combination drug and this result was statistically significant (p=0.02). Also, we did not find any significant heterogeneity in the included studies reporting progression free survival (I^2=40%, p=0.16).

Disease Progression Rate

Four studies reported on disease progression rate in both arms[16,17,19,20]. Except Mahner et al[19], all the other studies favour paclitaxel combination with pooled RR of 0.87 with 95% CI: 0.61-1.24 (Figure 4). This shows that the evidence is not conclusive to tell which method results in decreased disease progression rate. It shows that the PLD combination is non-inferior to paclitaxel combination in disease progression rate. We did not find any heterogeneity among the studies reporting disease progression rate (I^2=0%, p=0.95).

Overall Response Rate (ORR)

Among the studies[16,17,19,20] included in the review, four studies reported an overall response rate in both arms[16,17,19,20]. Except Mahner et al[19], all the other studies favour paclitaxel combination with pooled RR of 1.07 with 95% CI: 0.94-1.20 (Figure 5A). This shows that the overall response rate was better for paclitaxel combination when compared to PLD combination. However, this result was not statistically significant (p=0.31). We did not find any heterogeneity among the studies reporting disease progression rate (I^2=0%, p=0.54).

Complete Response Rate

Three studies reported on complete response rate in both groups[16,17,20]. The pooled RR was 1.00 (95% CI: 0.61-1.63) (Figure 5B). This shows that there was no significant difference between

Table II. Risk of bias assessment for the included studies, N = 7.

S. No	Author and year	Random sequence generation	Allocation concealment	Blinding of the participants, outcome assessment	Incomplete outcome data	Selective reporting of outcome	Other risk of bias
1.	Bafaloukos 2010[16]	Low risk	Low risk	High risk	Low risk	Unclear risk	Low risk
2.	Gladieff 2012[17]	Low risk	Low risk	High risk	Low risk	High risk	Low risk
3.	Kurtz 2011[18]	Low risk	Low risk	High risk	Low risk	High risk	Low risk
4.	Mahner 2014[19]	Low risk	Low risk	High risk	Low risk	High risk	Low risk
5.	Pignata 2011[20]	Low risk	Low risk	High risk	Low risk	Unclear risk	Low risk
6.	Pujade-Lauraine, 2010[7]	Low risk	Low risk	High risk	Low risk	High risk	Low risk
7.	Wagner 2012[21]	Low risk	Low risk	High risk	Low risk	High risk	Low risk

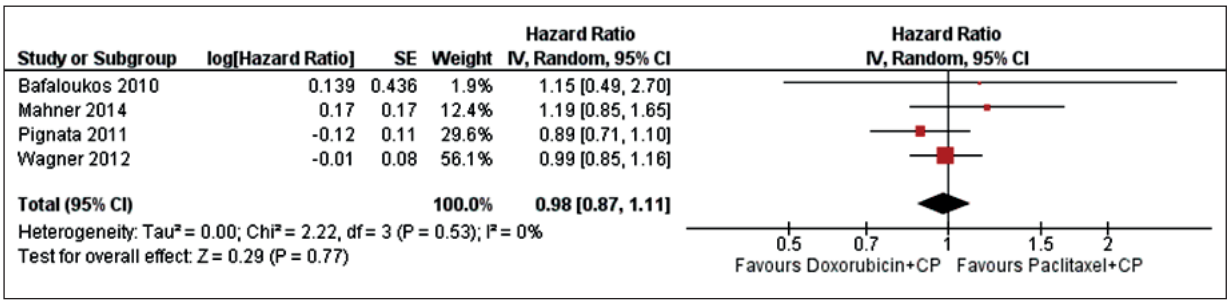

Figure 2. Forest plot showing the difference in overall survival between paclitaxel and PLE combination therapy (n=4).

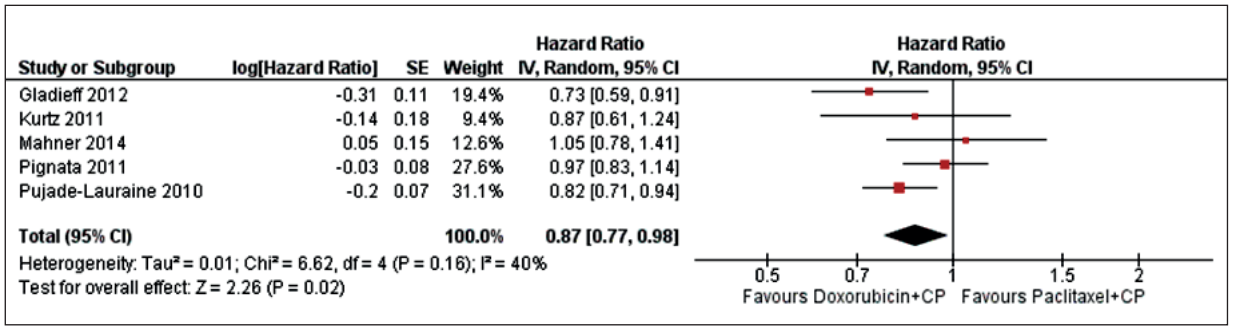

Figure 3. Forest plot showing the difference in progression free survival between paclitaxel and PLE combination therapy (n=5).

the two groups in terms of complete response rate (p=0.99). There was moderate heterogeneity among the studies reporting complete response rate (I^2=58%, p=0.09).

Partial Response Rate

Three studies reported on partial response rate in both groups[16,17,20]. The pooled RR was 1.14 (95% CI: 0.91-1.44) (Figure 5C). Here also, there is no conclusive evidence to prove that the paclitaxel combination is superior to PLD combination (p=0.26). There was mild heterogeneity among the studies reporting partial response rate, but it was not statistically significant (I^2=29%, p=0.25).

Disease Control Rate

Two studies reported on disease control rate in both arms[16,17]. The pooled RR was 1.03 (95% CI: 0.93-1.13) favouring the paclitaxel combination, but the result was not statistically significant (p=0.61) (Figure 6). We did not find any heterogeneity among the studies reporting disease control rate (I^2=0%, p=0.34).

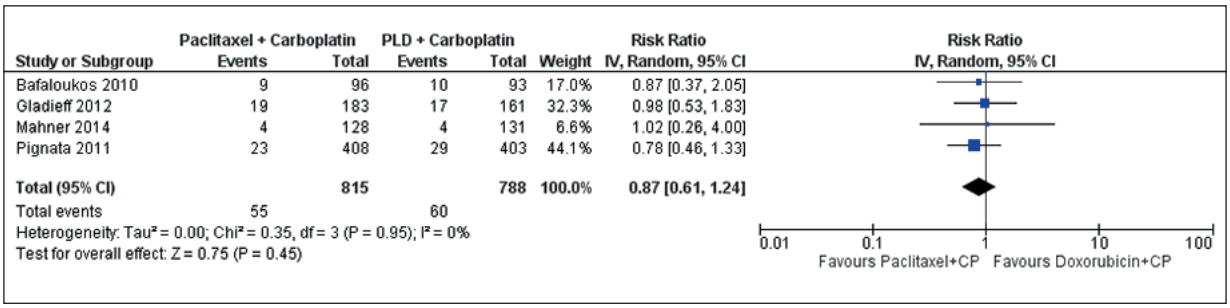

Figure 4. Forest plot showing the difference in disease progression rate between paclitaxel and PLE combination therapy (n=4).

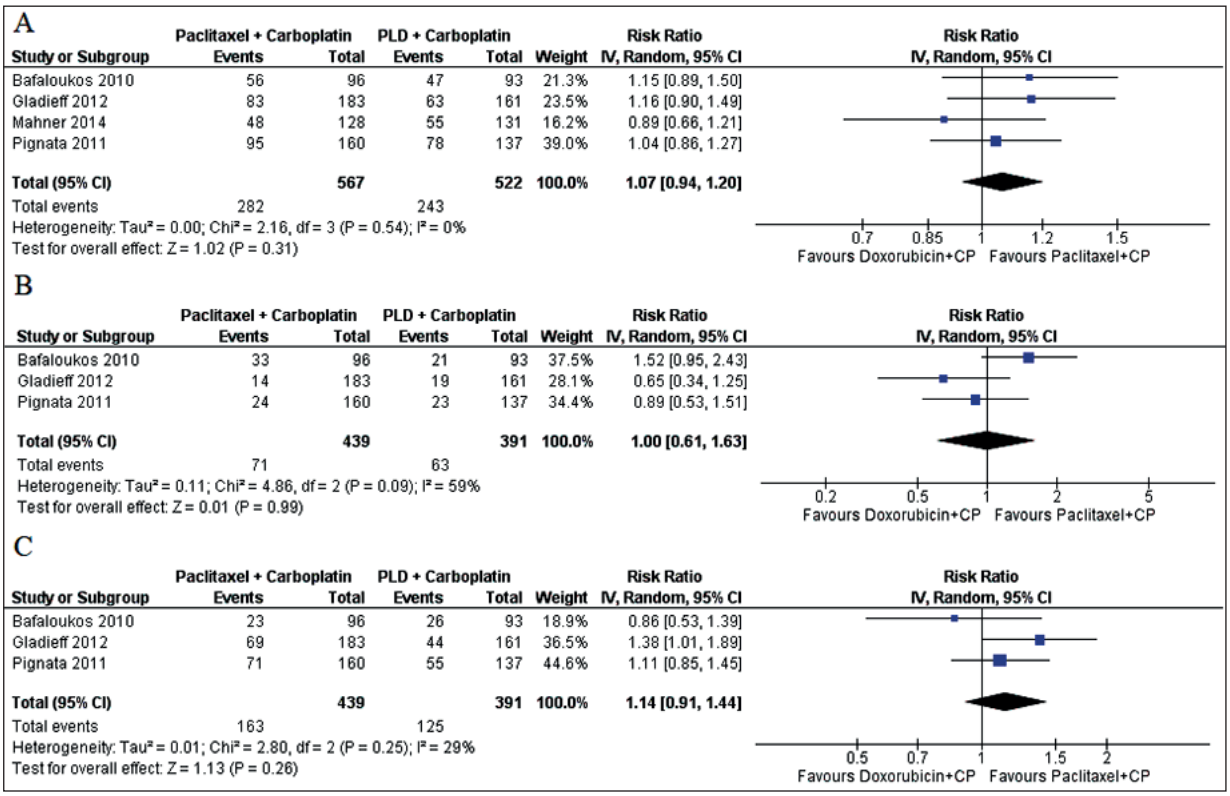

Figure 5. **A**, Forest plot showing the difference in overall response rate between paclitaxel and PLE combination therapy (n=4). **B**, Forest plot showing the difference in complete response rate between paclitaxel and PLE combination therapy (n=3). **C**, Forest plot showing the difference in partial response rate between paclitaxel and PLE combination therapy (n=3).

Toxicity Profile

Toxicity profile was assessed for the worst grade symptoms (≥ Grade 3 symptoms) alone between both groups. We compared the incidence of hematological and non-hematological manifestations following the treatment in both groups.

Hematological Manifestations

Anemia

Six studies reported on the incidence of anemia in both groups[7,16-20]. The pooled RR was 0.52 (95% CI: 0.38-0.70) favouring the paclitaxel combination patients (Figure 7A). This shows that ovarian cancer patients taking paclitaxel combination had 48% less chance of developing anemia when compared to PLD combination patients and this result was statistically significant ($p<0.001$). Also, we did not find any heterogeneity among the studies reporting anemia incidence following treatment ($I^2=0\%$, $p=0.52$).

Leukopenia

Three studies reported on the incidence of leukopenia in both groups[16,19,20]. All the studies

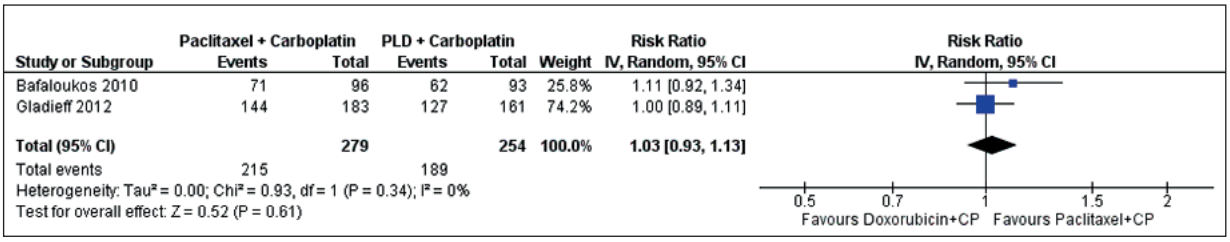

Figure 6. Forest plot showing the differrence in disease control rate between paclitaxel and PLE combination therapy (n=2).

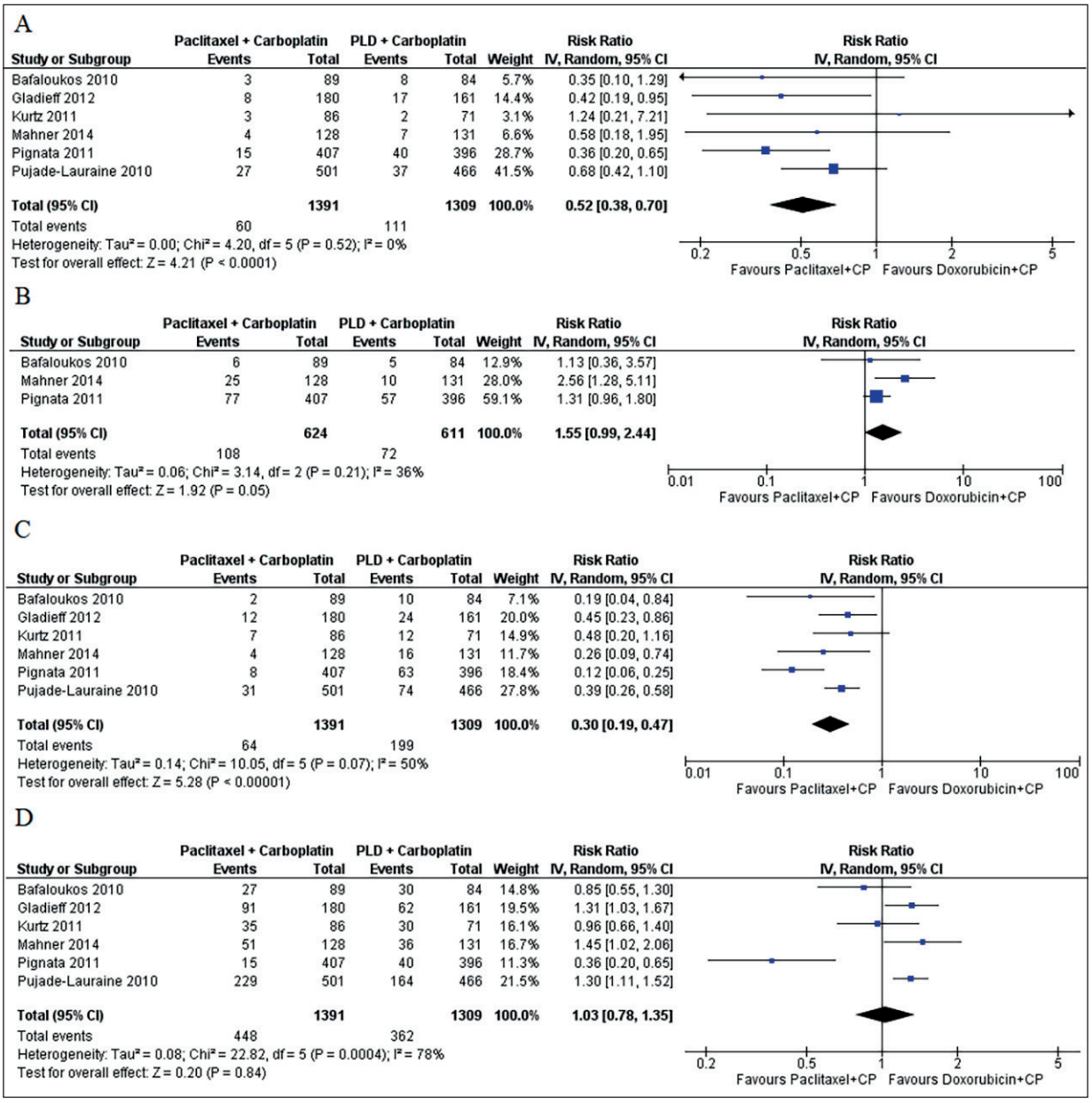

Figure 7. A, Forest plot showing the difference in anemia incidence between paclitaxel and PLE combination therapy (n=6). **B**, Forest plot showing the difference in leukopenia incidence between paclitaxel and PLE combination therapy (n=3). **C**, Forest plot showing the difference in thrombocytopenia incidence between paclitaxel and PLE combination therapy (n=6). **D**, Forest plot showing the difference in neutropenia incidence between paclitaxel and PLE combination therapy (n=6).

reported that the patients receiving paclitaxel combination have more chance of developing leukopenia. The pooled RR was 1.55 (95% CI: 0.99-2.44) favouring the PLD combination patients (Figure 7B). This shows that the results are not statistically significant. We found mild heterogeneity among the studies reporting leukopenia prevalence following treatment (I^2=36%, p=0.21).

Thrombocytopenia

Six studies reported on the prevalence of thrombocytopenia in both groups[7,16-20]. All the studies reported results favouring the patients receiving paclitaxel combination. The pooled RR was 0.30 (95% CI: 0.19-0.47) (Figure 7C). This shows that the patients receiving paclitaxel combination therapy have significantly lesser risk of developing thrombocytopenia during the treat-

ment when compared to patients receiving PLD combination therapy ($p<0.001$). We found moderate heterogeneity among the studies reporting thrombocytopenia incidence following treatment ($I^2=50\%$, $p=0.07$).

Neutropenia

Six studies reported on the incidence of neutropenia following the treatment in both groups[7,16-20]. Half the studies reported results favouring the patients receiving paclitaxel combination and rest half favoured PLD combination. The pooled RR was 1.03 (95% CI: 0.78-1.35) (Figure 7D). This shows that there is no statistically significant difference between the two groups in terms of neutropenia incidence following treatment ($p=0.84$). We found significant heterogeneity among the studies reporting neutropenia incidence following treatment ($I^2=78\%$, $p<0.001$).

Non-Hematological Manifestations

Nausea/Vomiting

Five studies reported on the incidence of nausea/vomiting during combination chemotherapy in both groups[1,7,16,19,20]. Except Mahner et al[19], all other studies favoured paclitaxel combination therapy. The pooled RR was 0.66 (95% CI: 0.32-1.37) (Figure 8A). These estimates show that there is no conclusive evidence in determining the risk of nausea/vomiting between the groups ($p=0.27$). There was a significant heterogeneity among the studies reporting nausea/vomiting ($I^2=63\%$, $p=0.04$).

Fatigue

Five studies reported on the incidence of fatigue during combination chemotherapy in both groups[1,7,16,19,20]. All the studies favoured paclitaxel combination therapy. However, the pooled RR was 0.84 (95% CI: 0.53-1.34) (Figure 8B). These estimates show that there is no conclusive evidence in determining the risk of fatigue between the groups ($p=0.48$). There was no heterogeneity among the studies reporting fatigue ($I^2=0\%$, $p=0.76$).

Allergy

Six studies reported on the incidence of allergy during combination chemotherapy in both groups[7,16-20]. Except Bafaloukos et al[16], all other studies favoured PLD combination therapy. The pooled RR was 1.86 (95% CI: 1.06-3.24) (Figure 8C). This shows that patients receiving paclitaxel combination therapy have 1.86 times higher risk of developing allergy during the treatment when compared to PLD combination therapy and this was statistically significant ($p=0.03$). There was no heterogeneity among the studies reporting allergy ($I^2=0\%$, $p=0.40$).

Neurotoxicity

Six studies reported on the incidence of neurotoxicity during combination chemotherapy in both groups[7,16-20]. All the studies favoured PLD combination therapy. The pooled RR was 5.59 (95% CI: 1.43-21.84) (Figure 8D). This shows that patients receiving paclitaxel combination therapy has 5.59 times higher risk of developing neurotoxicity during the treatment when compared to PLD combination therapy and this was statistically significant ($p=0.01$). There was mild heterogeneity among the studies reporting neurotoxicity, but it was not statistically significant ($I^2=41\%$, $p=0.17$).

Cardiotoxicity

Four studies reported on the incidence of cardiotoxicity during combination chemotherapy in both groups[7,16,17,20]. The pooled RR was 0.51 (95% CI: 0.06-3.99) (Figure 8E). This shows that there is no conclusive evidence in determining the risk of cardiotoxicity between the two groups ($p=0.52$). There was moderate heterogeneity among the studies reporting neurotoxicity, but it was not statistically significant ($I^2=56\%$, $p=0.13$).

Discussion

The management of ovarian cancer has varied historically and is grade-dependent. However, platinum agents like carboplatin in combination with paclitaxel have been commonly used in the treatment of ovarian cancer for high grade patients. These agents have their own advantage and disadvantages. PLD has been proven to be a safer alternative with minimal toxicity and equivalent efficacy in trials conducted around the world. However, there is a lack of systematic and high-quality research comparing these two combination chemotherapeutic agents directly. Hence, we conducted this review to compare the efficacy and safety of PLD + carboplatin and paclitaxel + carboplatin, in terms of outcomes such as overall survival, progression free survival, disease progression, and control rate, overall response rate (both complete and partial) and toxicity profile

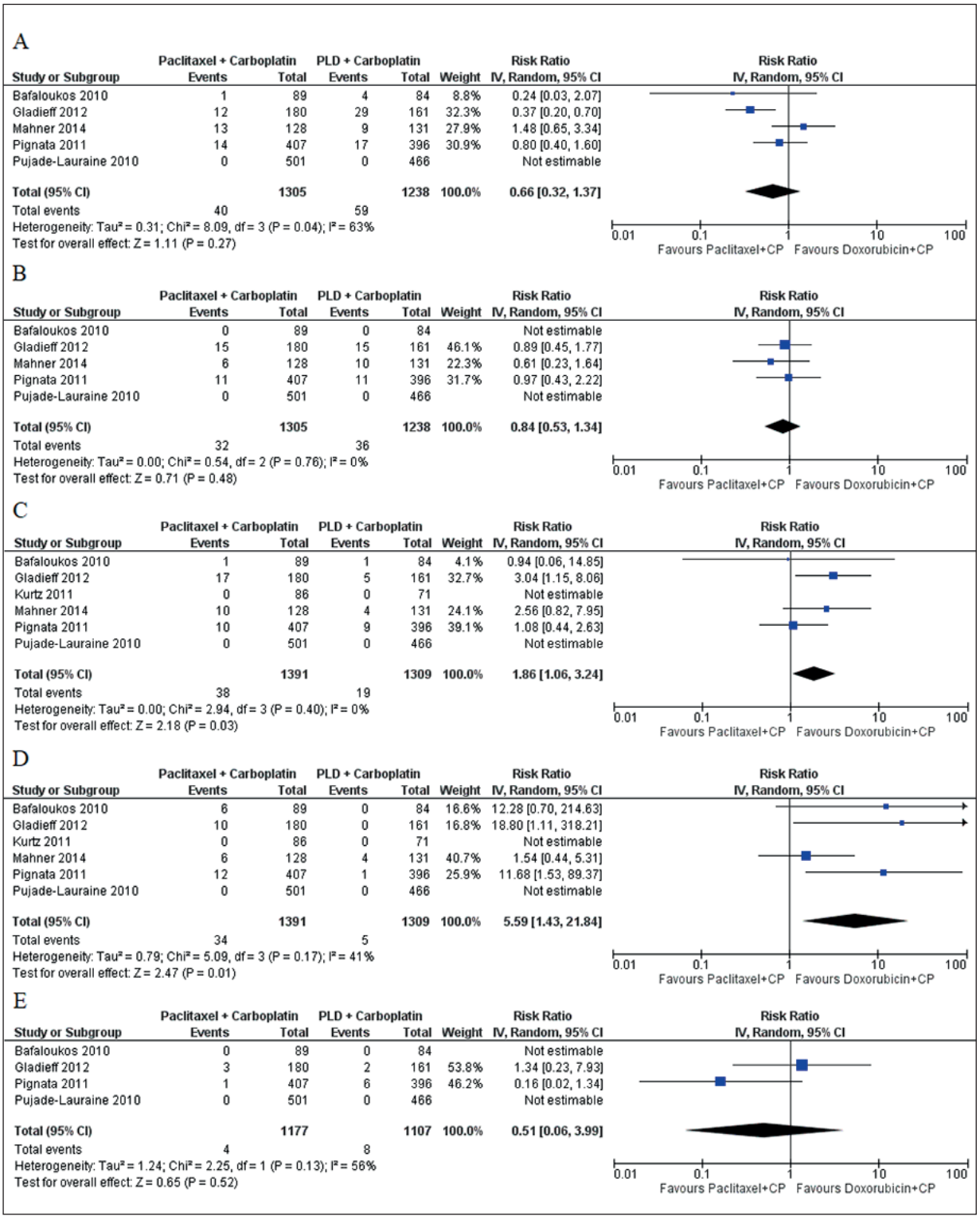

Figure 8. **A**, Forest plot showing the difference in nausea/vomiting incidence between paclitaxel and PLE combination therapy (n=5). **B**, Forest plot showing the difference in fatigue incidence between paclitaxel and PLE combination therapy (n=5). **C,** Forest plot showing the difference in allergy incidence between paclitaxel and PLE combination therapy (n=6). **D**, Forest plot showing the difference in neurotoxicity incidence between paclitaxel and PLE combination therapy. (n=6) **E**, Forest plot showing the difference in cardiotoxicity incidence between paclitaxel and PLE combination therapy (n=4).

(both hematological and non-hematological). We tried to compile the best possible evidence available up to date to compare these medications.

In all, we identified 7 studies with 3,676 participants for our analysis. Out of these, five trials were part of larger multi-national RCTs conducted in 16 countries across the continents of Europe, North America, Australia, and Middle Eastern countries. Most of the studies in our review had low risk of bias[7,16,17,19,20]. We did not find any substantial heterogeneity among the reported outcomes in the studies. Hence, subgroup analysis or meta-regression was not performed to explore the source of heterogeneity. Main outcomes such as overall survival and progression free survival were found to be better for PLD combination therapy while other outcomes like disease progression rate, disease control rate, and overall response rate favoured the paclitaxel combination therapy. However, we did not find conclusive or significant evidence for any of these outcomes except progression free survival (favoured PLD combination therapy) as the confidence limit crossed the null value in all the other outcomes assessed. This shows that PLD combination therapy is superior to paclitaxel combination therapy in progression free survival while it is non-inferior to paclitaxel therapy in relation to other outcomes.

Mixed response was found in relation to the worst grade toxicity profile. Except leukopenia, all other hematological toxicities were higher among patients receiving PLD combination therapy. Similarly, non-hematological toxicities such as fatigue, nausea/vomiting, and cardiotoxicity were higher among patients receiving PLD combination therapy. However, none of these toxicities showed statistically significant evidence. While other toxicities like allergy and neurotoxicity were significantly higher among patients receiving paclitaxel combination therapy when compared to patients receiving PLD combination therapy. This again shows that PLD combination therapy is non-inferior to paclitaxel combination therapy in terms of toxicity profile (both hematological and non-hematological).

The major strengths of our study include the comprehensive search of literature and the broad search strategy to gather all the required publications up-to-date. Ours is the first review directly comparing the prognosis (survival) outcomes and toxicity profile between PLD and paclitaxel combination therapy for the management of ovarian cancer patients. A network meta-analysis conducted by Jiang et al[22] compared only three studies and had limited number of outcomes assessed. Important outcomes such as overall survival and progression free survival were analysed in our review to provide conclusive evidence on efficacy of PLD combination therapy over paclitaxel combination therapy. We only included RCTs into our review which enables us to infer causal associations between the intervention and outcomes.

We are also aware of the limitations in our review. We included only 7 RCTs in our review. Hence, more RCTs with larger sample size should be done to gather more evidence. We could not assess for publication bias as the number of studies included in the review was less than 10 (minimum requirement to perform funnel plot or Egger's test). Finally, most of the studies included in our review were conducted in high income countries, which may limit the generalizability of our findings to other geographical regions.

Our study has certain implications towards clinical practice. We found that PLD combination therapy is non-inferior to the paclitaxel combination treatment in the management of ovarian cancer patients. Till now, paclitaxel combination therapy is widely used as first line chemotherapeutic agent to manage high grade ovarian cancer. Previous evidence has shown that paclitaxel combination therapy has potential adverse effects on the central nervous system of the patients causing residual neurotoxicity following the first line treatment[16,18]. It is known to negatively influence the quality of life of patients because of the cumulative toxicities.

With the current evidence, clinicians can use PLD combination therapy in place of paclitaxel as a reasonable alternative depending on the patient profile (i.e., if the patients are at high risk of neurotoxicity or allergy) or it can be used as an alternative if the patients on paclitaxel develop such side effects. However, uncertainties regarding efficacy and safety persist as some of the studies have inadequate sample size which limits the power of the studies. Apart from efficacy and safety concerns, questions related to dose response relationship to determine the optimal dose and schedule for treatment require further exploration. To develop conclusive evidence on these factors, more robust RCTs or prospective studies with larger sample size are needed to strengthen the evidence for recommendations on how to best treat ovarian cancer patients using standard chemotherapeutic regimens.

Conclusions

In summary, PLD combination therapy is non-inferior to paclitaxel combination therapy in the management of ovarian cancer with respect to survival outcomes and worst grade toxicity profile. However, more robust RCTs with large sample size are required to derive conclusive evidence towards efficacy, safety, and dose response relationship of PLD and paclitaxel combination chemotherapy.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contribution

SS and FJ designed the paper. TH, YZ, LC, and XH were involved in literature search and data interpreted. SS, FJ, and TH were responsible for the data analysis. SS and FJ prepared the manuscript. All authors have read and approved the final manuscript.

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