SAFETY AND EFFICACY OF CISPLATIN COMBINATIONS WITH VINORELBINE, PACLITAXEL AND GEMCITABINE – A SYSTEMATIC REVIEW AND META-ANALYSIS

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy Hons

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I/We have acknowledged all main sources of help.

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Approval

The thesis titled “Safety and efficacy of cisplatin combinations with vinorelbine, paclitaxel and gemcitabine – a systematic review and meta-analysis” submitted by Inaya Islam 19146026, of Spring, 2023 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy

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Ethics Statement

This study does not include any animals or human trails.

Abstract

Introduction: The aim of the study is to assess the efficacy of cisplatin combinations with paclitaxel, gemcitabine and vinorelbine for the first line treatment of non-small cell lung cancer.

Methods: The Cochrane library, PubMed. ClinicalTrials.gov were used to retrieve report. The included clinical trials and randomized controlled trials (RCT) were evaluated for hazard ratios of the overall survival (OS) and Progression Free Survival (PFS). The statistical analysis was performed using JASP and CMA. PRISMA guidelines were used to evaluate the methodology.

Results: The hazard ratio found for CV, CG and CP are 0.76 (0.68,0.84), 0.88 (0.79,0.97) and 0.81 (0.65,0.97) respectively for OS and 0.71 (0.47,0.96), 0.69 (0.43,0.96) and = 0.65 (0.53,0.77) for PFS respectively. The hazard ratio of the subgroup analysis of OS and PFS of all combinations is HR = 0.825 (0.806,0.894) and HR =0.694 (0.563,0.856) respectively.

Conclusions: cisplatin combined with vinorelbine, gemcitabine, and paclitaxel have shown statically significant improved efficacy and safety in terms of treatment of NSCLC as compared to other available treatments

Keywords: NSCLC, paclitaxel, cisplatin, gemcitabine, vinorelbine, meta-analysis

Acknowledgement

I would like to start by thanking God, because without His guidance this would not have been possible. I would also especially like to thank my professor Dr. Mohd. Raeed Jamiruddin who supervised me throughout this whole thesis and guided me with patience and words of affirmation. I would also like to thank anyone who supported me throughout this whole process

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List of Acronyms

NSCLC	Non-small cell lung cancer
OS	Overall survival
PFS	Progression free survival
HR	Hazard ratio
CV	Cisplatin + Vinorelbine
CG	Cisplatin + Gemcitabine
CP	Cisplatin + Paclitaxel

Chapter 1

Introduction

Lung cancer is one of the most common cancers contributing to cancer-related mortality worldwide (Sabbula et al., 2022). Lung cancer originates from the mutation of the squamous cells lining the air passages of the lungs which is primarily caused by tobacco smoke.(Sabbula et al., 2022) It is divided into two main subtypes: small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC)(DeLozier et al., 2014). Non-small cell lung cancer (NSCLC) is responsible for about 85% of all lung cancers(Griesinger et al., 2019). Surgery is usually seen as the preferred treatment, however only about 20% to 25% of tumors are suitable for resection, hence other treatment options need to be explored (Datta & Lahiri, 2003)

For newly diagnosed non-small-cell lung cancer (NSCLC), about two-thirds of patients have an advanced stage of the disease (stage IIIB or IV) and this can only be treated with palliative chemotherapy. However, according to several randomized studies and a meta-analysis, chemotherapy is advantageous rather than palliative care alone for enhancing the quality of life and overall survival (OS)(Brodowicz et al., 2006). Furthermore, a published data-based meta-analysis demonstrated that the addition of a second drug to a single-agent chemotherapy regimen resulted in a statistically significant increase in the objective tumor response rate (Pallis et al., 2013), Hence a doublet regimen is preferred to be followed. Current ASCO guidelines for NSCLC claim that platinum-based doublets are to be preferred over non-platinum ones due to their higher response rate and their marginal OS superiority, furthermore recommends the use of cisplatin over carboplatin whenever it is possible (Pallis et al., 2013)

The standard first-line drug therapy for advanced NSCLC, neoadjuvant, adjuvant, or chemoradiotherapy is usually a second or third-generation cytotoxic drug combined with a platinum-based agent such as cisplatin or carboplatin.(DeLozier et al., 2014) .The new-

generation cytotoxic agents used are gemcitabine, vinorelbine, paclitaxel, or docetaxel (Bunn, 2002)Considering first-line platinum-based combinations enhance survival, minimize symptoms, and improve quality of life, they are preferred first-line choices for NSCLC chemotherapy(Buccheri et al., 2006)

For this study, cisplatin has been chosen as the platinum-based agent due to its preference as previously mentioned, and a meta-analysis was carried out for three combinations. The purpose of this study is to compare the efficacy and toxicity of three platinum-based combination regimens, cisplatin plus paclitaxel (PC), cisplatin plus gemcitabine (CG), cisplatin plus vinorelbine (CV).

No clinical trials have previously been carried out where these specific combinations have been tested. One similar study- a Four-Arm Cooperative Study in Japan - which came close was conducted by Y Ohe et al where they compared the efficacy and toxicity of cisplatin plus irinotecan (IP) versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine, however, their results showed similar efficacy and different toxicity profiles. To address these inconsistencies about the effectiveness and side effects of these regimens, we carried out a systematic meta-analysis of randomized controlled trials, which compared these three platinum-based doublets to find the most effective regimen

Chapter 2

Methodology

2.1 Eligibility Criteria

Inclusion criteria for patients: All the patients were histologically or pathologically confirmed to have locally advanced non-small cell lung cancer. Patients of all age groups were included in the test

Exclusion criteria for patients: Patients who received any other anticancer drug adjuvant to the tested combination.

Inclusion criteria for study design: randomized controlled trial (RCT), clinical trials, a meta-analysis of the cisplatin doublets regimens versus other regimens such as single, double, triplets, or observation.

Exclusion criteria for study design: a cohort study, case report, review articles, letters, and low-quality clinical research were excluded.

The outcome measures were the HR values of PFS and OS. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines

2.2 Information Sources

We searched bibliographic databases such as PubMed, trial registries like ClinicalTrials.gov, iiar-anticancer.org, open access journal databases like lungcancerjournal.info - from inception to June 2023, for only English language for articles published ranging from 1997-2023

2.3 Search Strategy

We searched all published clinical trial articles in Pubmed databases between January 1997 and February 2023, and also searched with keywords:

((((cisplatin) AND (nsclc)) AND (vinorelbine)) AND (gemcitabine)) AND (paclitaxel)

(((nsclc) AND (cisplatin)) AND (chemotherapy)) AND (vinorelbine)AND (hazard ratio)

(((nsclc) AND (cisplatin)) AND (chemotherapy)) AND (paclitaxel)AND (hazard ratio)

(((nsclc) AND (cisplatin)) AND (chemotherapy)) AND (gemcitabine)AND (hazard ratio)

Filters used - clinical trials, meta-analysis, randomized controlled trial

Search strategy	Number of results
((((cisplatin) AND (nsclc)) AND (vinorelbine)) AND (gemcitabine)) AND (paclitaxel)	49
(((nsclc) AND (cisplatin)) AND (chemotherapy)) AND (vinorelbine)AND (hazard ratio)	46
(((nsclc) AND (cisplatin)) AND (chemotherapy)) AND (paclitaxel)AND (hazard ratio)	39
(((nsclc) AND (cisplatin)) AND (chemotherapy)) AND (gemcitabine)AND (hazard ratio)	70

2.4 Selection Process

Initially, the selection was conducted by screening through abstracts and titles, followed by careful examination of the full articles using the exclusion and inclusion criteria. The second reviewer ensured the articles followed the eligibility criteria.

2.5 Data Collection Process

Data were extracted from several eligible trials and listed on an Excel sheet. The following data of all eligible trials were extracted: name of the article and its DOI, name of the first author, publication year, number of enrolled patients, overall survival rate (OS), Progression-free survival (PFS), Hazard Ratio (HR)

2.6 Study Risk of Bias Assessment

To evaluate the quality of the study we used the Cochrane Handbook. It was used to evaluate the bias arising from the following aspects: randomization process, intended interventions, missing outcome data, outcome measurement, selective reporting, and other sources of bias. Each aspect was labeled as high-risk, unclear risk, or low-risk. A second reviewer was consulted to determine eligibility if any disagreements arise

2.7 Statistical Analyses

The statistical analyses in this analysis were carried out using JASP statistical software. The classical meta-analysis option was used. The model was estimated using Restricted ML Method. Hence the calculation of p value was approximate along with the determination of a fixed or random effects model type was automatically carried out by the software. Publication

bias was analyzed and presented by funnel plots using regression test for funnel plot asymmetry. Sub group analysis of three treatment groups were carried out using the software comprehensive meta-analysis (CMA)

Chapter 3

Results

3.1 Selection of Trials

215 studies were identified after the initial search. Among them, only 23 trials were included in this meta-analysis according to relevance to the study and those which matched the eligibility criterias. From those studies we extracted the hazard ratios of the OS and PFS of the desired drugs against the others experimented which we regarded as the controls

3.2 S[illegible] Results

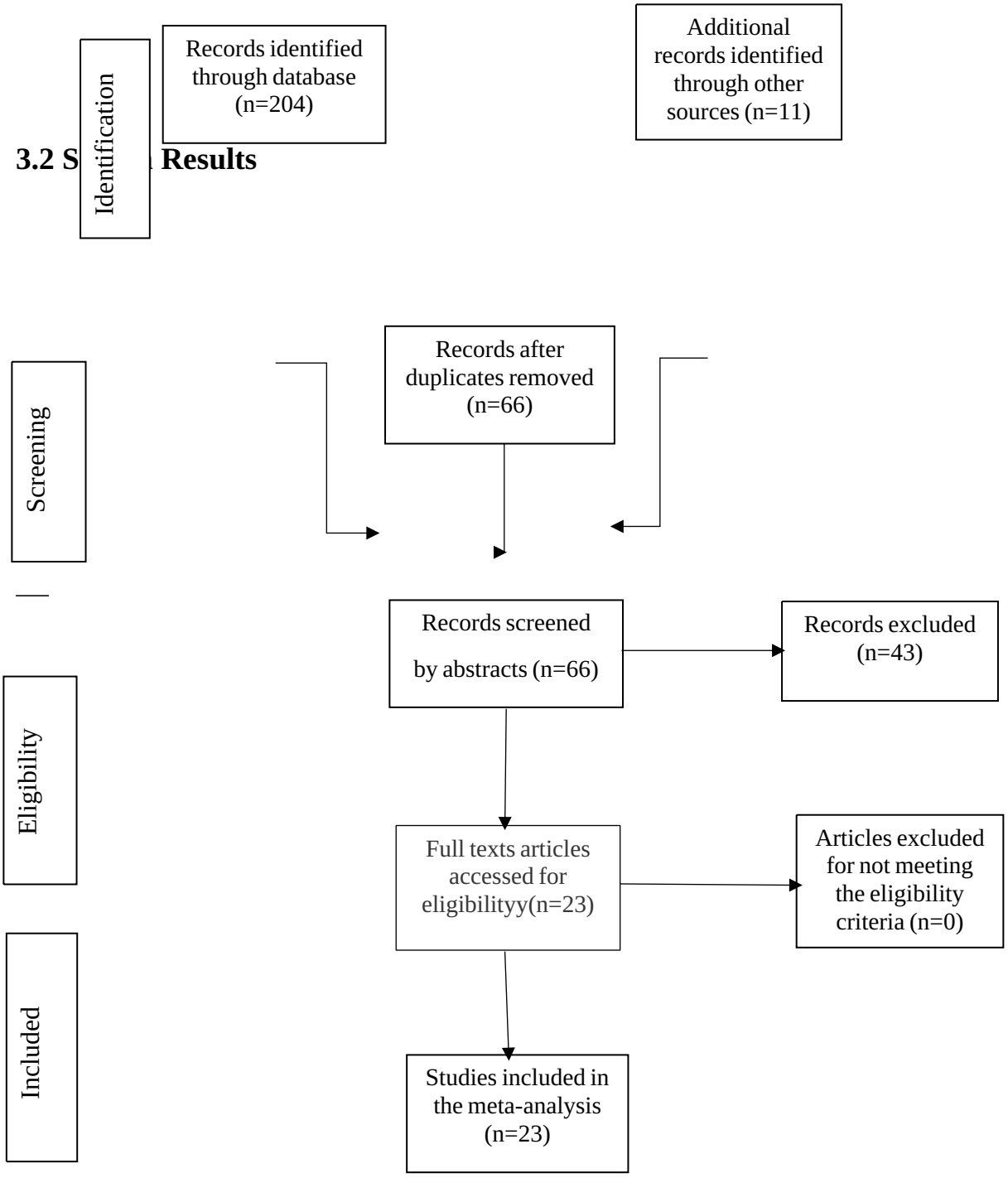
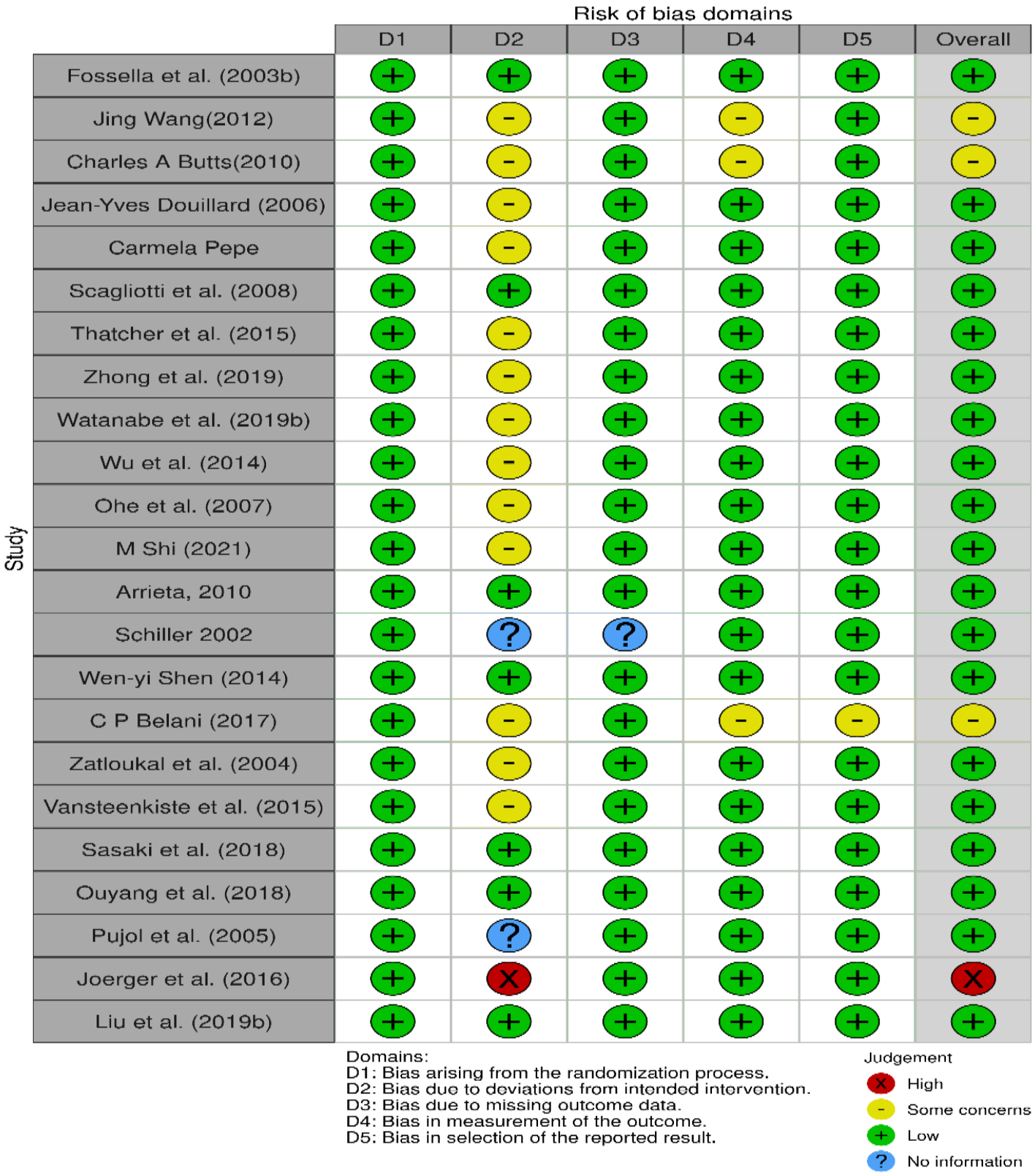


Fig 1. Flowchart of the selection process

A total of 215 articles were found and 149 articles were excluded because they were duplicates or did not meet the eligibility criteria. Further detailed assessment of abstracts and full texts

screened out 43 records. Finally, 23 trials involving advanced NSCLC patients were included in this meta-analysis



3.3 Risk of Bias

Fig 2. Risk of bias table: review of authors' judgments about each risk of bias item for included studies

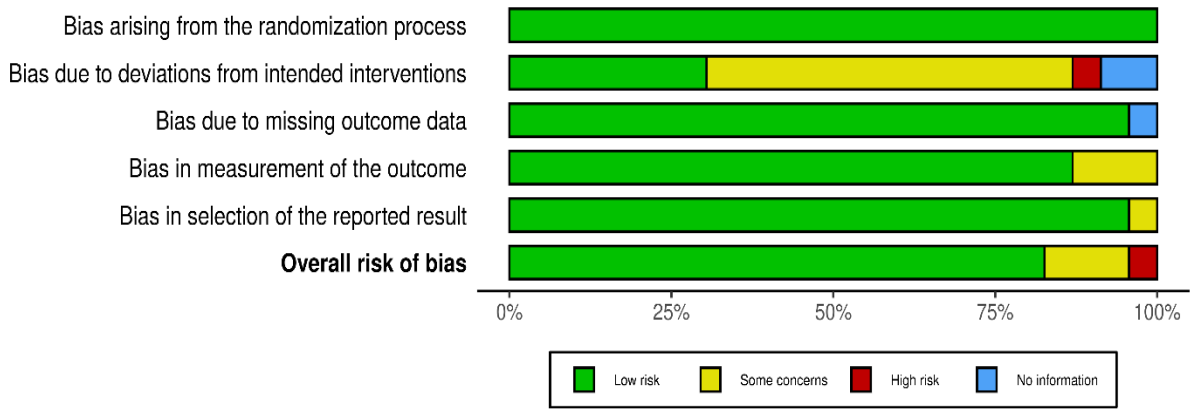


Fig 3. Risk of bias graph: overview of authors' judgments about each risk of bias item presented as percentages across all included studies.

A risk assessment of bias assessment was carried out for all the trials included in the study using robvis tool online. Randomization of allocation was low risk and well concealed for all the studies. Two of the studies did not have complete information about the blinding process. The study by Joergar et al. (2016) was classified as high risk as it was an open-label study. Thirteen other studies were classified with some concerns due to being open label yet being a comparative study with automized randomization. Overall, selective reporting was not identified for only one study – Schiller (2002). Most of the studies has low risk in terms of bias of reported result and outcome measurement. The overall risk of bias was labelled low.

3.4 Results of meta-analysis

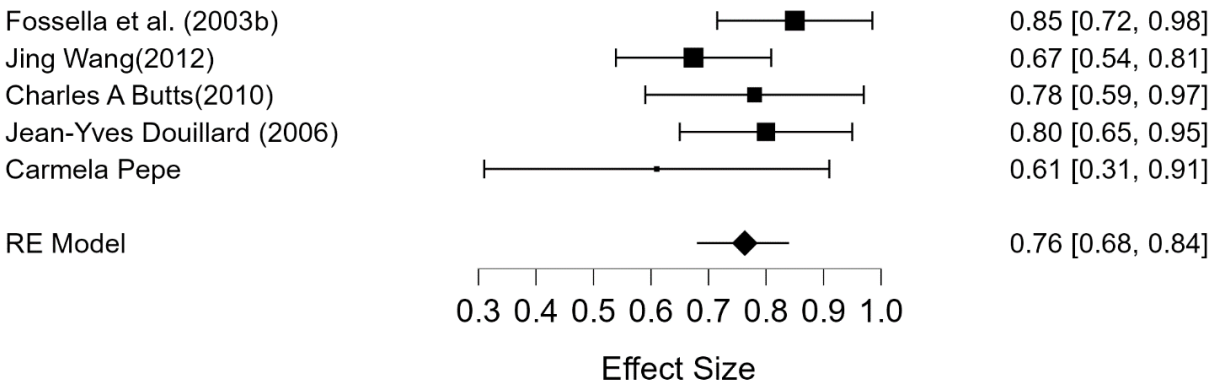


Fig 4. Forest plot of overall survival of cisplatin + vinorelbine (OS)

The hazard ratio of the OS of vinorelbine is HR = 0.76 (0.68,0.84), in the forest plot obtained since the diamond is on the left side of the line of no effect, it can therefore be concluded that the trials prefer the experimental side which is the drug vinorelbine and not the control.

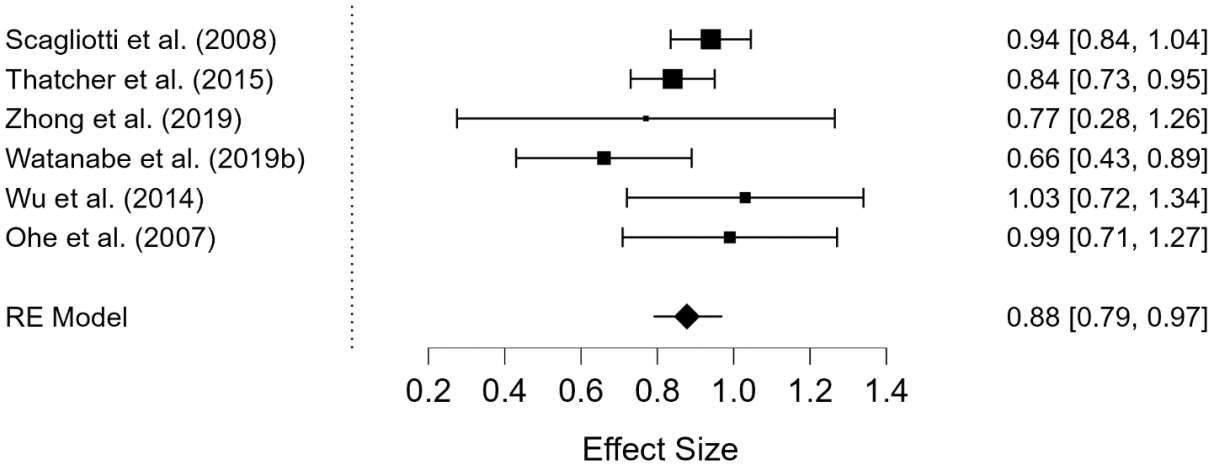


Fig 5. Forest plot of overall survival of cisplatin + gemcitabine (OS)

The hazard ratio of the OS of gemcitabine is HR = 0.88 (0.79,0.97), in the forest plot obtained, since the diamond is on the left side of the line of no effect, it can therefore be concluded that

the trials prefer the experimental side which is the drug gemcitabine and not the control.

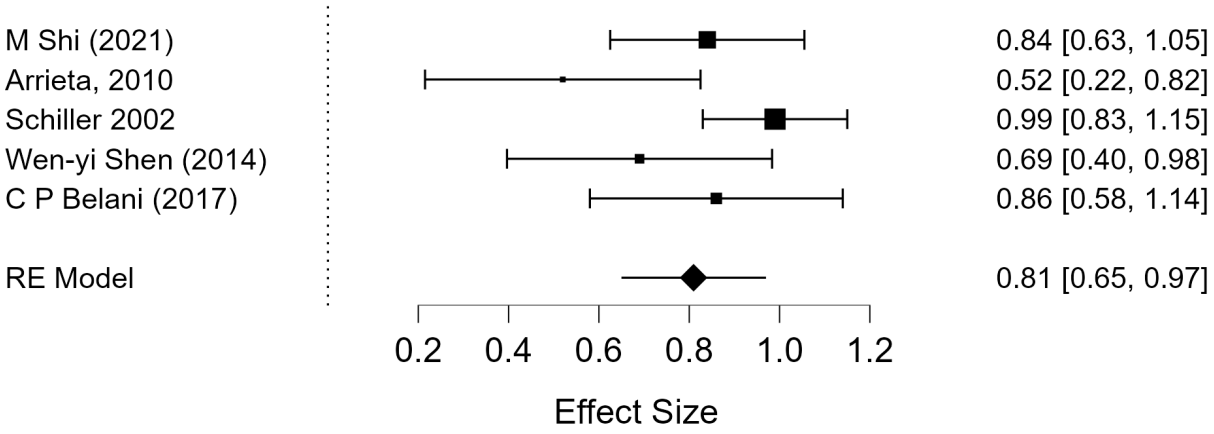


Fig 6. Forest plot of overall survival of cisplatin + paclitaxel (OS)

The hazard ratio of the OS of paclitaxel is HR = 0.81 (0.65,0.97), in the forest plot obtained, since the diamond is on the left side of the line of no effect, it can therefore be concluded that the trials prefer the experimental side which is the drug paclitaxel and not the control.

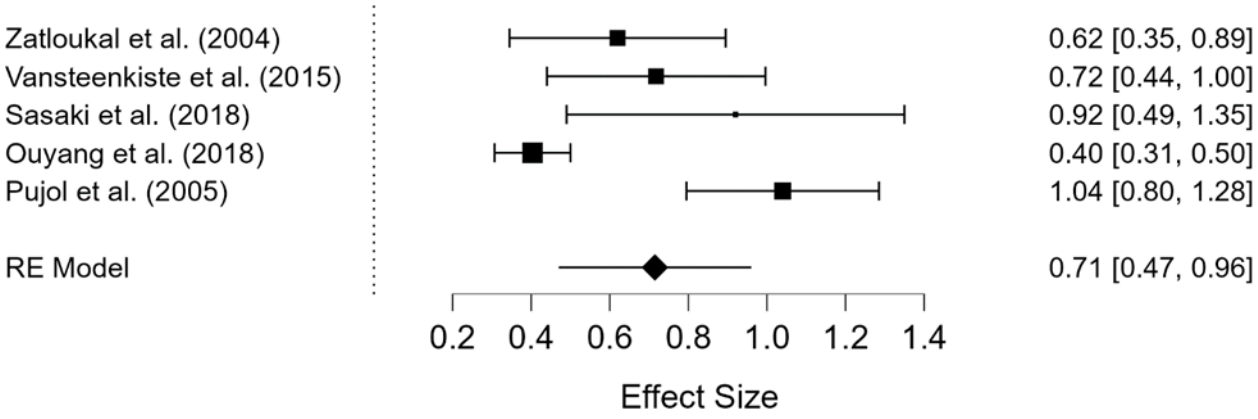


Fig 7. Forest plot of progression free survival of cisplatin + vinorelbine (OS)

The hazard ratio of the PFS of vinorelbine is HR = 0.71 (0.47,0.96), in the forest plot obtained, since the diamond is on the left side of the line of no effect, it can therefore be concluded that the trials prefer the experimental side which is the drug vinorelbine and not the control.

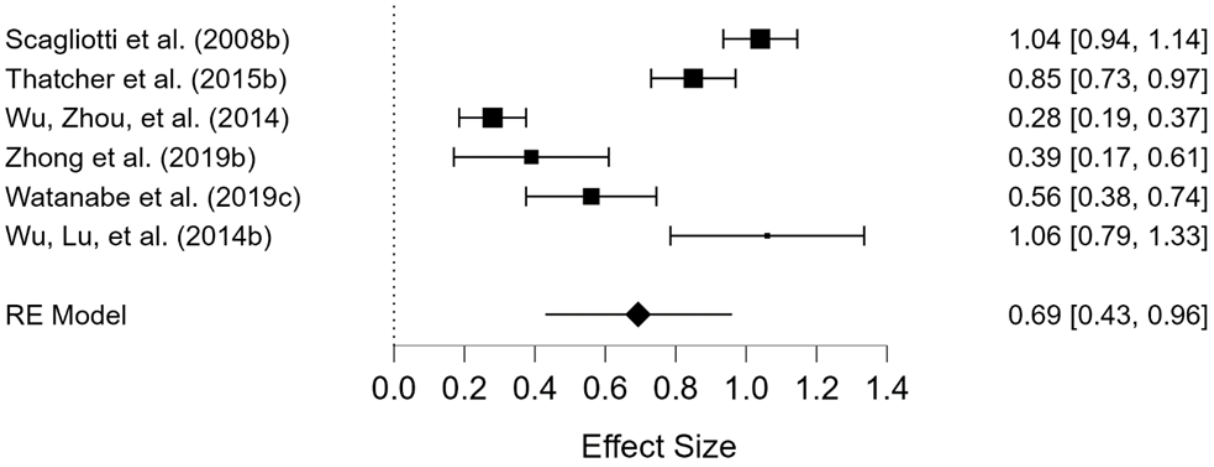


Fig 8. Forest plot of progression free survival of cisplatin + gemcitabine (OS)

The hazard ratio of the PFS of gemcitabine is HR = 0.69 (0.43,0.96), in the forest plot obtained, since the diamond is on the left side of the line of no effect, it can therefore be concluded that the trials prefer the experimental side which is the drug gemcitabine and not the control.

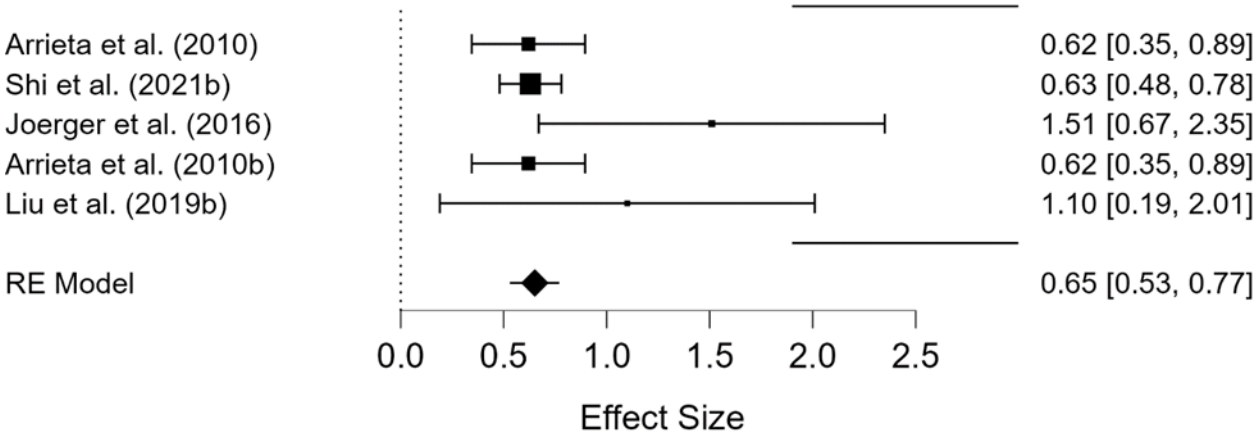


Fig 9. Forest plot of progression free survival of cisplatin + paclitaxel (OS)

The hazard ratio of the PFS of paclitaxel is HR = 0.65 (0.53,0.77), in the forest plot obtained, since the diamond is on the left side of the line of no effect, it can therefore be concluded that

the trials prefer the experimental side which is the drug paclitaxel and not the control.

Therefore since all the three drugs show advantage over the controls and their hazard ratio are of comparable value we can therefore conclude that these three drugs have comparable efficacy with little to no advantage over one another. The analysis of the OS and PFS showed no significant difference between the efficacy of the three drugs

3.5 Publication Bias

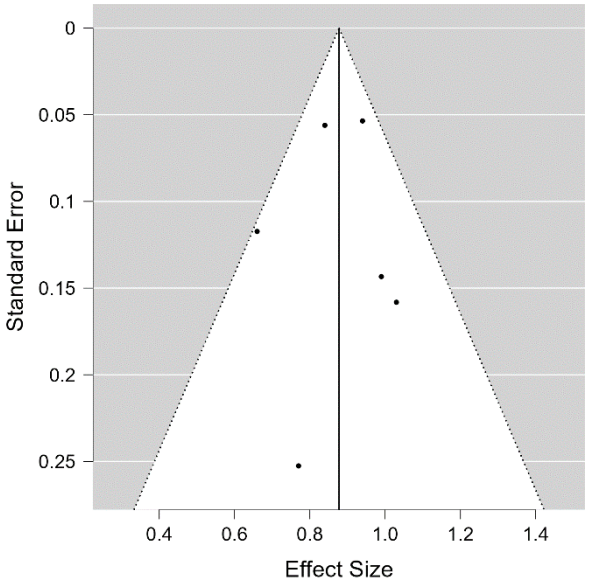


Fig 10. Funnel plot of OS of cisplatin + vinorelbine

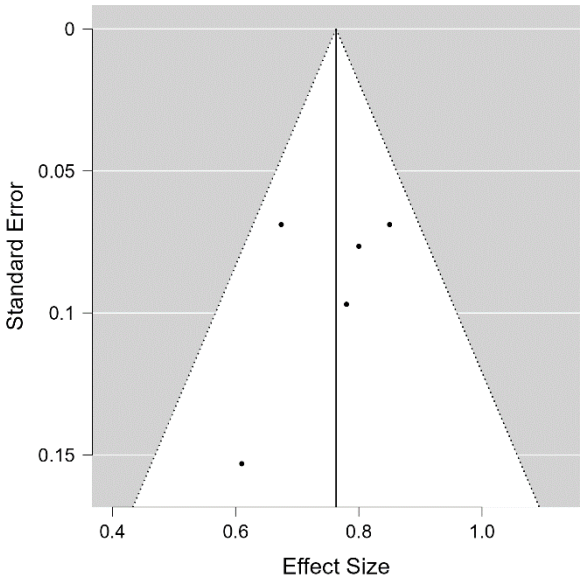


Fig 11. Funnel plot of OS of cisplatin +gemcitabine

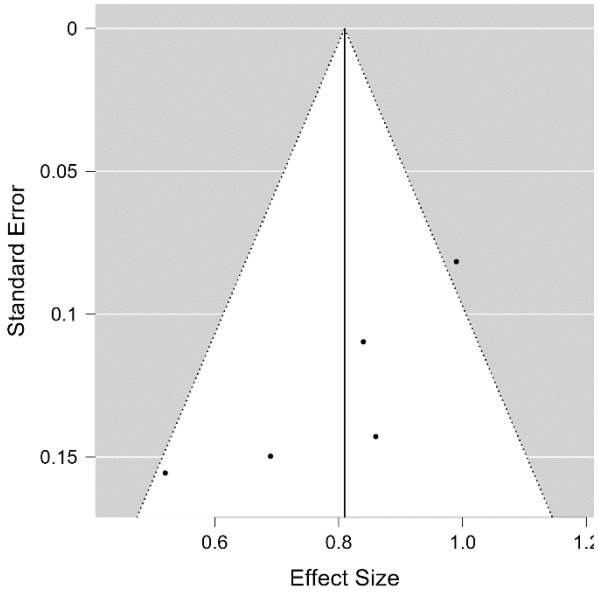


Fig 12. Funnel plot of OS of cisplatin +gemcitabine

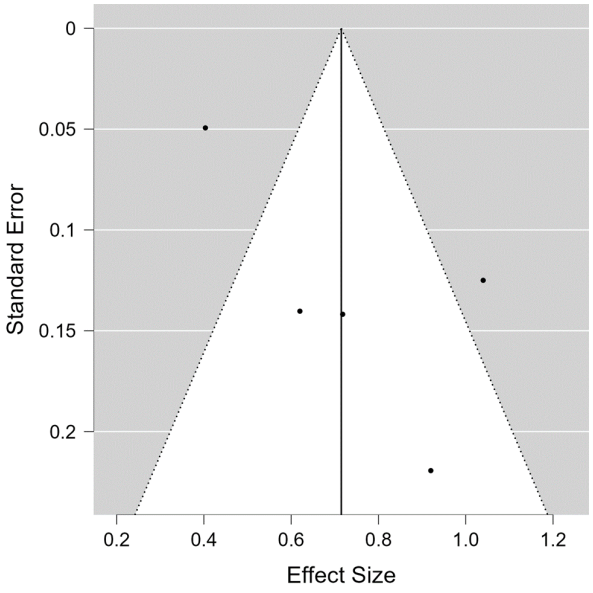


Fig 13.Funnel plot of PFS cisplatin +vinorelbine

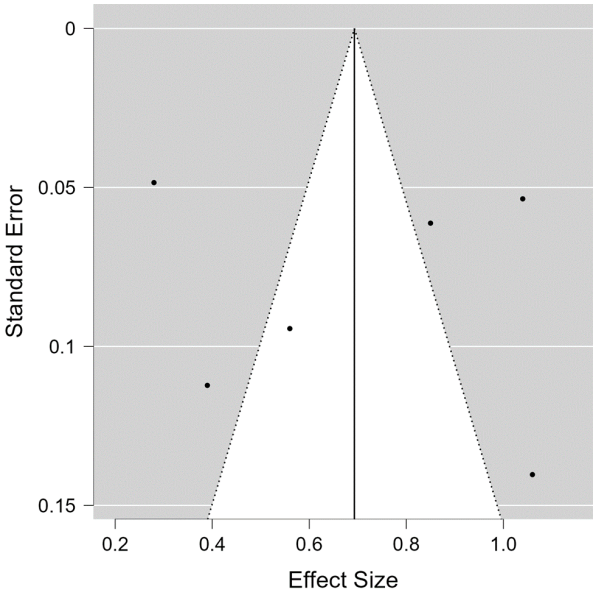


Fig 14.Funnel plot of PFS cisplatin+gemcitabin

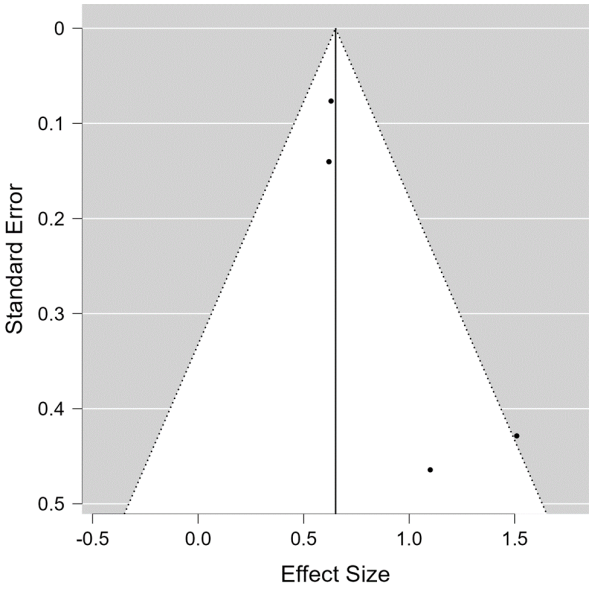


Fig 15.Funnel plot of PFS cisplatin +paclitaxel

Funnel plots based on OS and PFS were drawn with the standard error of HR as the vertical axis and HR value as the x-coordinate on the horizontal axis. The distribution of scattered points on both sides of the line were approximately symmetrical, and the overall distribution was moderately uniform, indicating that the publication bias of the study was relatively small and hence reliable

3.6 Results of subgroup Analysis

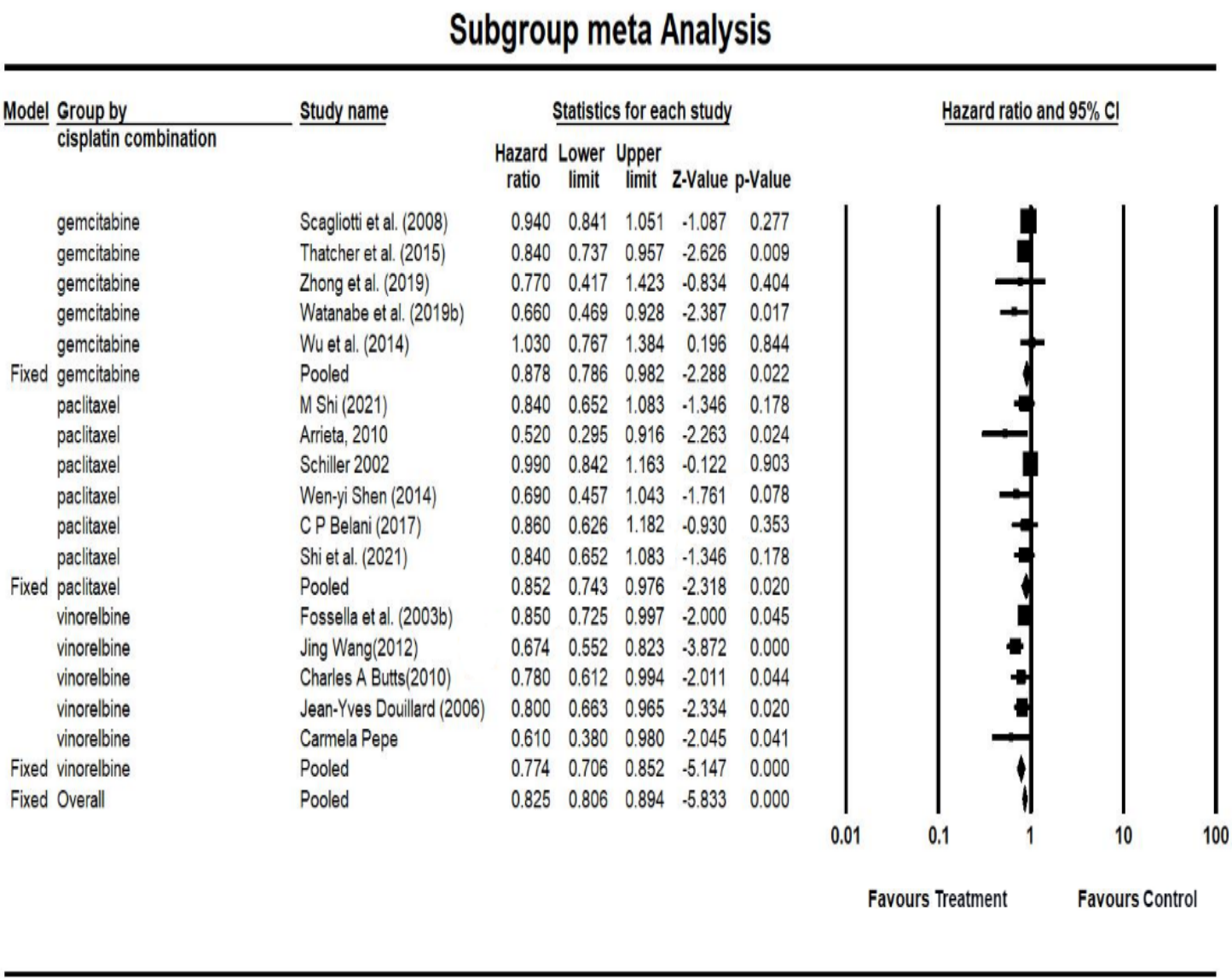


Fig 16.Forest plot of OS of subgroup pooled analysis

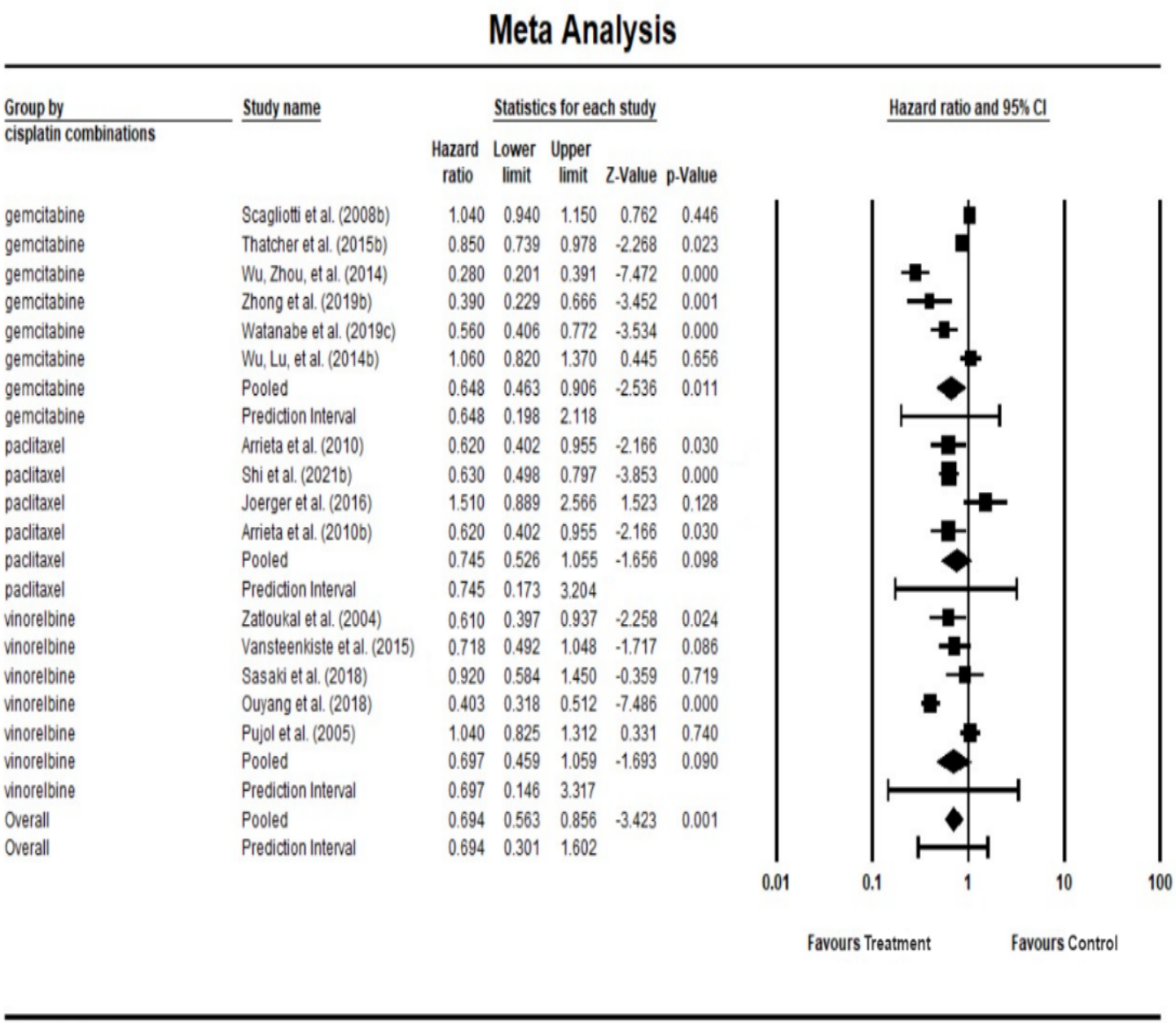


Fig 17.Forest plot of PFS of subgroup pooled analysis

In the forest plot obtained ,the hazard ratio of the subgroup analysis of OS and PFS of all combinations is HR = 0.825 (0.806,0.894) and HR =0.694 (0.563,0.856) respectively, since the diamond is on the left side of the line of no effect for both the plots , it can therefore be concluded that the included trials prefer the experimental side which are the cisplatin combinations and not the control

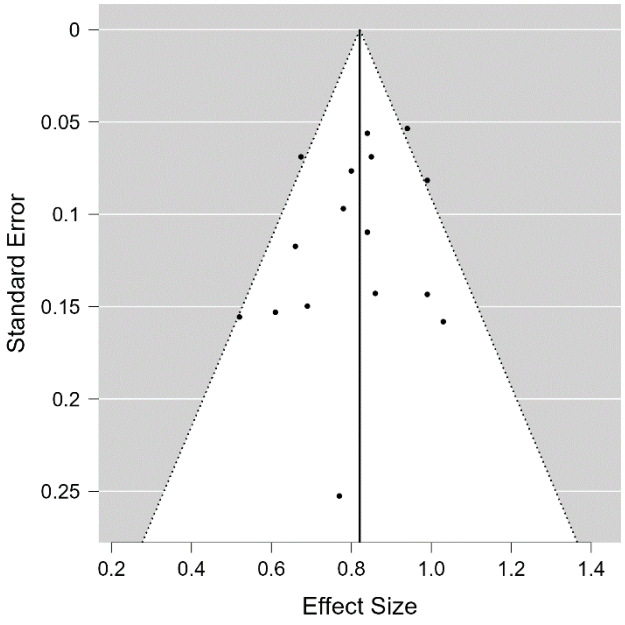


Fig 18.Funnel plot of OS of subgroup analysis

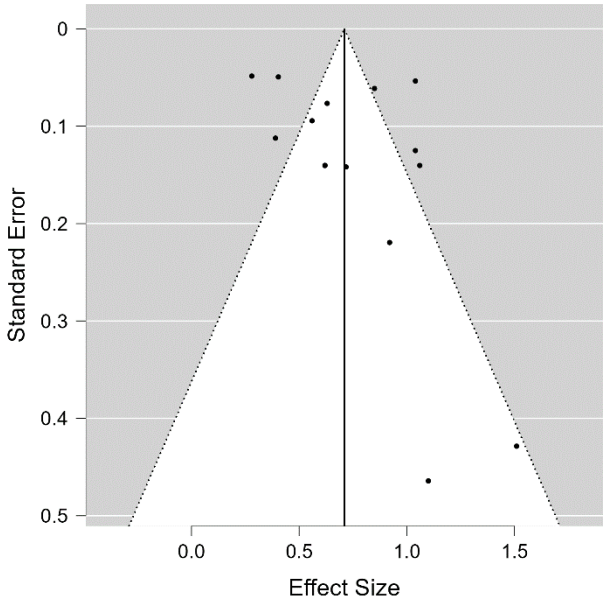


Fig 19.Funnel plot of PFS of subgroup analysis

Pooled funnel plots based on OS and PFS were drawn with the standard error of HR as the vertical axis and HR value as the x-coordinate on the horizontal axis. The distribution of scattered points on both sides of the line were approximately symmetrical, and the overall distribution was moderately uniform, indicating that the publication bias of the study was relatively small and hence reliable

Chapter 4

Discussion

The role of platinum combinations in the treatment of NSCLC has been questioned due to its toxic effects hence leading to low acceptability. (Pujol et al., 2006) Therefore, this meta-analysis was carried out to determine if platinum doublets regimens are effective and safe as compared to other acceptable alternatives. Overall survival and progression-free survival were used as the primary endpoint where their hazard ratios were extracted to determine efficacy. The combinations considered here were cisplatin combined with third-generation anticancer drugs such as vinorelbine gemcitabine and paclitaxel. the results of the forest plots of the individual drug combinations showed that the treatments were more favorable for the cisplatin combination group as compared with the other controls which were mostly observations or any other drug combination. Their hazard ratios were OS were 0.76,0.88,0.95 and for PFS were 0.71,0.65,0.69- this showed that their hazard ratios were not significantly different hence we can conclude that they have comparable efficacy. Furthermore, a subgroup analysis was performed where all the data of OS and PFS were pooled to form one determining hazard ratio. this survival analysis showed favor in terms of the treatment group as compared to the controls. the treatment groups being our cisplatin drug combinations. the result of OS is 0.774 and for PFS it is 0.694. The p values were 0.00 and 0.001 respectively indicating that the null hypothesis has been rejected and can therefore conclude that we t have sufficient evidence to say that our experimental drug combinations are therefore safer than the controls.

Two other similar meta-analyses were previously performed but were not significantly related to this one. However in one of those meta-analyses - the conclusion was that non-platinum doublets were as effective as platinum-based doublets with different toxicity profiles yet they did favor platinum doublets when they showed a significant advantage in PFS. (Jiang et al.,

2013)

In another meta-analysis performed the results indicated that a platinum-based doublet significantly reduced the risk of death when compared with non-platinum chemotherapy within an acceptable increase in toxicity- hence favoring my results further by proving its efficacy and safety. (Pujol et al., 2006)

One limitation of my experiment was my inability to keep the controls of my experiment consistent. this was due to the lack of previous experiments performed leading to a lack of data for me. This was however overcome by doing the subgroup analysis and assuming the overall advantage over a wide range of treatments.

4.1 Conclusion

In conclusion, we can assume that for the most part cisplatin-containing regimens such as cisplatin combined with vinorelbine, gemcitabine, and paclitaxel have shown statically significant improved efficacy and safety in terms of treatment of NSCLC as compared to other available treatments

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