“Comparing Effectiveness and Safety of combination therapy for Esophageal and Gastro Esophageal Junction Cancer: A Comprehensive Meta-Analysis”

By

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A thesis that was turned in to the School of Pharmacy to complete the criteria needed to get a Bachelor of Pharmacy (Hons.).

School of Pharmacy
Brac University
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Declaration

The statement affirms the following assertions:

1. The thesis that has been presented is an original work, exclusively undertaken for the purpose of fulfilling the requirements of the undergraduate degree program at Brac University.
2. This project work is not incorporated to any prior publishment or third-party authored material, unless appropriately acknowledged through exact referencing.
3. None of the previously reported or credited works were contained in this project at any other degree or credential, either from a university or any other institution.
4. All necessary sources of support were correctly acknowledged.

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Approval

The project titled "Comparing Effectiveness and Safety of combination therapy for Esophageal and Gastro Esophageal Junction Cancer: A Comprehensive Meta-Analysis" submitted by Shifaty Nur Abir (ID: 18346008) of Summer, 2018 has been acknowledged satisfactorily meeting the requirements for the Bachelor of Pharmacy on 31st December, 2023.

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Ethics Statement

Any live human or animal subjects were excluded from research in the creation of this project; instead, it makes use of preexisting data and analysis.

Abstract

Introduction: In cases of resectable esophageal cancer, neoadjuvant immune checkpoint inhibitors and chemotherapy have been examined. Nonetheless, conflicting findings have been found in subsequent research. Thus, meta-analysis was the main purpose to methodically evaluate the safety and effectiveness profiles of immune treatment and chemotherapy combinations in individuals with esophageal cancer (EPC) or gastro-esophageal junction cancer (GEJC).

Method: Through a combination of MeSH (Medical Subject Headings) and keyword searches, “esophageal cancer”, “chemotherapy combination”, and “immunotherapy combination” in several databases, including the Google scholar, Researchgate, PubMed, and ClinicalTrials.gov websites, several articles were thoroughly reviewed and clinical randomized controlled trials (RCTs) were gathered by 2022. The Cochrane Methods were used to standardize the selection process, collect data from the studies, and evaluate the superiority of evidence and risk of bias. The primary measures were the estimated 95% CIs for the hazard ratio (HR) and odds ratio (OR) for overall survival (OS), progression-free survival (PFS), overall adverse events (OAE), and severe adverse events (SAE). R studio was used to evaluate the results, and online RobVis was also used for bias analysis.

Result: This meta-analysis looked at 15 RCTs with a total of 4,021 individuals to determine the effectiveness and safety of immunotherapy and chemotherapy for esophageal cancer. The outcomes demonstrated that the chemotherapy and immunotherapy treatment was linked with an overall risk for OS [HR = 0.85, 95% CI: 0.72–1.00; p < 0.71], PFS [HR = 0.94, 95% CI: 0.80–1.11]; p < 0.001], SAE (OR) = [0.99, 95% CI: 0.58–1.70; p = 0.08] and OAE (OR) = [0.72, 95% CI: 0.36–1.44; p = <0.01]. To determine the final result, Random Effects Model was utilised. The adverse event profile consisted of a combination of severe forms, such as

anemia, thrombocytopenia, neutropenia, and diarrhea, among other types. Thankfully, toxicities were within tolerable limits.

Conclusion: This research indicates that individuals with advanced, untreatable, or metastatic EPC/GEJ who have not got any conventional prior treatment will clearly benefit from immunotherapy and chemotherapy combination. Nonetheless, there is a significant chance that immunotherapy and chemotherapy can cause adverse responses, therefore more research on the management of untreated, incurable, advanced, or metastatic EPC/GEJ is necessary.

Keywords: Esophageal Cancer treatment, Chemotherapy, Immunotherapy, Combination drug, Efficacy, Safety, Hazard ratio, Clinical outcome and Gastroesophageal cancer (GEJC).

Dedication

To my family and the war-stricken brothers and sisters of Palestine

Acknowledgement

I give thanks to Allah, the Most Powerful, for bestowing upon me the strength, patience, and dedication required to finalise this thesis work. This work would have been insurmountable without the direction and assistance from several individuals to whom I owe my sincerest respect.

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Table of Contents

List of Tables

List of Figures

List of Abbreviations

EPC	Esophageal Cancer
GEJC	Gastro-Esophageal Cancer
GC	Gastric Cancer
OS	Overall Survival
PFS	Progression Free Survival
SAE	Severe Adverse Events
OAE	Overall Adverse Events
CAP + CIS	Capecitabine plus Cisplatin
PAC + CARBO	Paclitaxel plus Carboplatin
NIVO + IPI	Nivolumab plus Ipilimumab
HR	Hazard Ratio
OR	Odds Ratio
CI	Confidence Interval
RCT	Randomized Controlled Trial
CT	Chemotherapy
RT	Radiotherapy
ICI	Immune Checkpoint Inhibitors

Chapter 1: Introduction

1.1 Background

Over half a million people per year (5.5% of all cancer deaths) are now related to esophageal cancer (Sung et al., 2021). For nearly fifty years, surgical processes have been the typical treatment for esophageal cancer. Patients' risk of dying during surgery has decreased dramatically due to the progress of new technology and the expansion of research into novel cancer targets (Ajani et al., 2019). For few years, exclusively in several European nations and the USA, the frequency of esophageal squamous cell carcinoma and adenocarcinoma has diminished, but the occurrence of gastro-esophageal junction adenocarcinoma (GEJ) has slowly progressed to a concerning level (Torre et al., 2016). There is indication to suggest that EPC and GEJ share comparable treatment methods due to their shared molecular similarities and clinical responses to different chemotherapy in metastatic situations. In the absence of a universal approach, the Siewert categorization of GEJ into esophageal cancer kinds is commonly employed (Siewert et al., 2000). This arrangement is theorized on the position of the tumor center relative to the inner diameter of the esophagus. Similar cells can be found in these cell membranes, which can lead to cancer. Unfortunately, endoscopic differentiation of the tumor's center is hampered by the fact that some tumors of the gastroesophageal junction span the entire length of these esophageal components. Although surgical excision remains the gold standard for treating GEJ today (Greally et al., 2019). So, to increase removal rate and the overall remedy rate of individuals, multimodal treatments involving chemotherapy, and other preoperative and postoperative medicines are progressively developed.

1.2 Chemotherapy Treatment

One study found that patients who underwent surgery followed by epirubicin before surgery and cisplatin with fluorouracil (ECF) had an increased 5-year overall survival rate than those who underwent surgery alone comparing 36% vs. 23%. The HR is 0.75 and 95% CI is 0.60-

0.93; p = 0.02 (Cunningham, 2006). The OS, median relapse free survival, tumor shrinkage, and R0 resection rate were all enhanced when patients received the chemotherapy regimen FLOT before surgery, which consists of platinum, other drugs and docetaxel, according to the FLOT4-AIO trial (Al-Batran et al., 2019). Preoperative chemoradiotherapy was found to improve median OS by 49 compared with 24 months, two and five year OS by 67% to 50%; overall 47% versus 34% with HR = 0.665, and the R0 surgery rate was 92% compared with 69% in the CROSS study, which compared how well neoadjuvant chemotherapy, radiation treatment, and surgery work on their own (Shapiro et al., 2015). However, from a meta-analysis it was found that both neoadjuvant chemoradiotherapy and neoadjuvant immunotherapy substantially increased survival rate by 2 years compared with resection alone with HR 0.81, 95% CI is 0.70 - 0.93 and p value is 0.002; and HR = 0.90, 95% CI is 0.81 - 1.00 with p value 0.05 (Gebski et al., 2007). These results give a rationale for developing treatments for GEJ cancer. However, 5-FU or platinum chemotherapy treatments had an average OS less than 12 months for unresectable advanced gastro-esophageal carcinoma (Kang et al., 2009). There is still a need for more research into the chemotherapeutic combinations.

1.3 Immunotherapy Treatment

Immunotherapy on the other hand has slowly shown novel perspectives on how to treat esophageal cancer. Programmed cell death-1 (PD-1) is expressed by many distinct types of immune cells. Autoimmunity and autoimmune T cells are protected from the effects of infection mostly by this mechanism. Tumor micro-infiltrating cells express PD-1, which allows the tumor to evade immune surveillance and avoid being destroyed by attaching to programmed death ligand-1 (PD-L1) (Ajani et al., 2022; Park et al., 2008). Hence, immunosuppressor drugs pointing the PD-1 path give a new route for therapy. Two types of cancers which are small cell lung cancer and melanoma benefit greatly from this therapy. Median OS in patients who had fatal GEJ cancer was significantly longer in the nivolumab arm of the ATTRACTION-2 trial

(5.26 vs 4.14 months) when compared to the placebo arm. The OS rate at 12 months was 26.2% vs 10.9%, and the PFS rate at 12 months was 7.6% vs 1.5%. (Ajani et al., 2005). Pembrolizumab's antitumor effectiveness and safety were both established in the KEYNOTE-059 trial (Han et al., 2020). In addition to their cytotoxic effects, chemotherapeutic drugs may also affect immune system, block immunosuppressor cells, therefore triggering immune effector cells and promoting an antineoplastic immune feedback, as described in several investigations (Baba et al., 2020; Xia et al., 2019). Immunotherapy for EPS shows promise, however not without immune-related adversities which include aenemia, rash, leukopenia and fatigue. Therefore, the reliability of immunotherapy versus chemotherapy is worthy of research and comparison. Inoperable patients with advanced or metastatic gastro-esophageal cancer have a poor diagnosis, thus it is important to investigate if chemotherapy combination or PD-1 inhibitor combinations will considerably improve their prognosis.

1.4 Objectives and Aims

While numerous trials have examined the effectiveness of PD-1 inhibitors and chemotherapy in treating advanced, inoperable, and metastatic EPC/GEJ, the results are inconsistent when compared to chemotherapy only (Janjigian et al., 2021). Therefore, a comprehensive analysis is needed to determine if these combined treatments offer significant benefits. In this research, data were compiled and reviewed from available articles, comparing the effectiveness and safety of combinations of both immuno and chemo therapy. The objective of this study is to produce a solid suggestion base in treating untreated, inoperable or metastatic EPC or GEJC.

Chapter 2: Methodology

2.1 Database Searches

This study followed the PRISMA extended report for meta-analyses. Using PubMed, Google Scholar, Researchgate, and the Clinical Trials of Controlled studies, all randomized studies published up to January 2022 were searched online. The search terms were “Esophageal or Gastro-esophageal” and “Clinical trial” and “Hazard Ratio” as well as “Chemotherapy” and “Immunotherapy” and “Randomized control trial”. This study included these eligibility requirements: (a) randomized phase 2-3 trials; (b) patients with locally advanced GEJ or EPC; (c) trials comparing preoperative CT plus or minus RT with surgical treatment alone or neoadjuvant CT; and (d) trials reporting OS and PFS and associated HRs with 95 percent CIs of intention-to-treat individuals only. Review trials, investigational medications, and past iterations of identical studies were excluded.

The quality of the included articles was evaluated with the online Cochrane risk-of-bias tool (RoBVis tool). OS was most important, followed by PFS, SAE, and OAE. The Q test and I^2 statistics assessed study heterogeneity. A random effects model with an I^2 value outside 50% was chosen. R Studio (Version 2023.09.0 Build 463) was used to meta-analyse and visualise the data. Based on HRs, each therapy’s survival chance was ranked.

2.2 Criteria for Inclusion and Exclusion

Articles were considered if phase ii or iii randomized controlled trials (RCTs) for individuals with histologically established EPC or GEJ (including inner line gastric cancer) undergoing adjuvant chemotherapy and immunotherapy. Only trials reporting on at least 2 of the following outcomes were considered: OS, PFS, SAE and OAE. Individuals with other cancers, for example ampullary cancer, were not considered for inclusion if the RCTs involved advanced or metastatic EPC/GEJ.

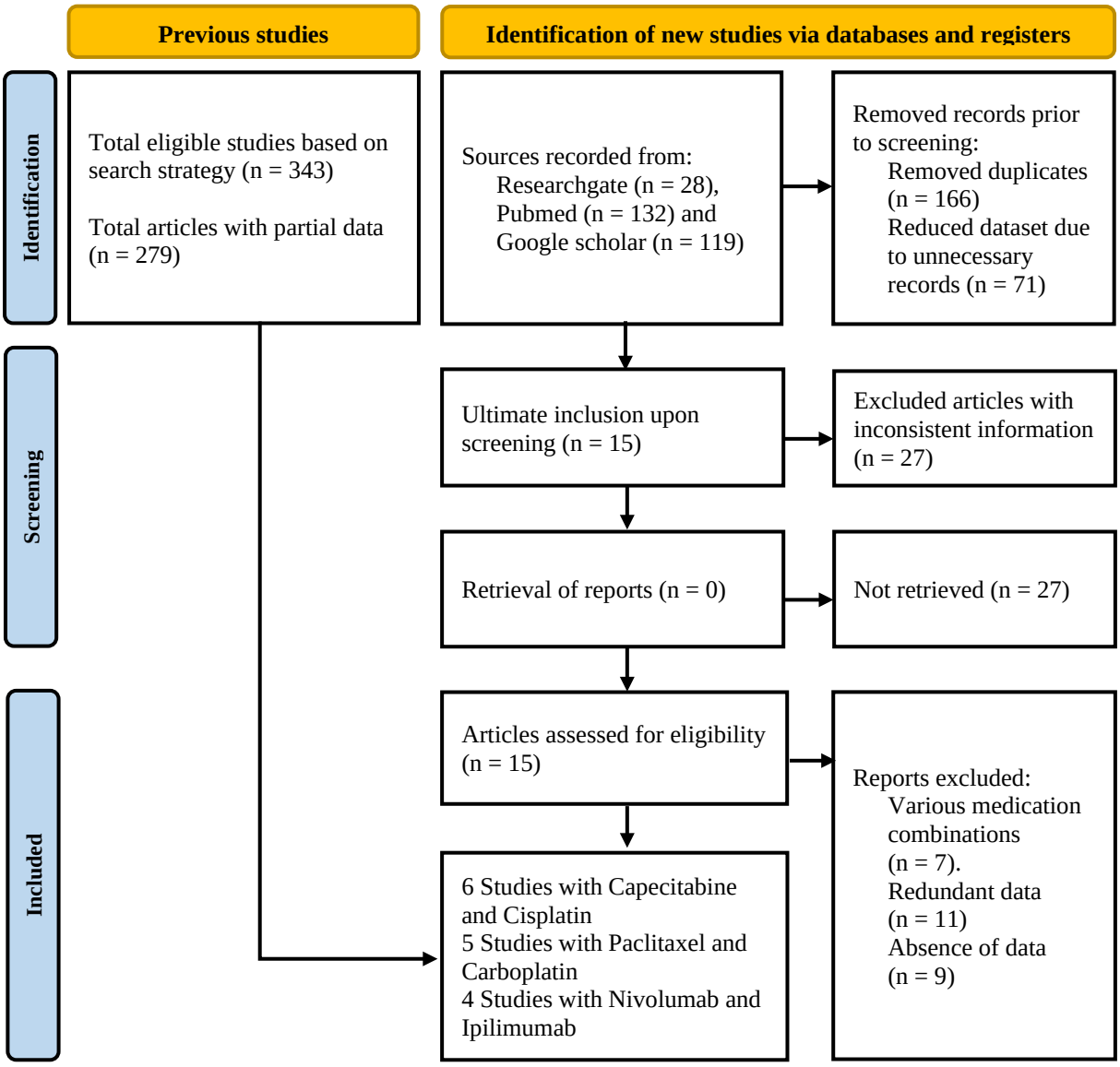

Table 1: PRISMA flow chart for the included and excluded studies

2.3 Extraction of Relevant Data

From the paper, we gathered information about OS, PFS, SAE, and OAE. Upper and lower limits of confidence intervals and hazard ratios were provided. For both OS and PFS, we also calculated the standard deviation, median, and maximum and minimum values. Nonetheless, solely the hazard ratios and adverse events remained as absolute necessities in the end. This study does not include any secondary outcomes. Time to first relapse was defined as the amount of time that had passed since the patient's initial diagnosis of cancer.

2.4 Statistical analysis

In this meta-analysis HRs and CIs were pooled using random-effects models. Heterogeneity was calculated with Q and I^2 statistics. If p value was >0.1 or I^2 was <50%, heterogeneity was statistically significant. No sensitivity analyses were done due to the tiny sample size. All statistical tests were done in R Studio [(Build 463), Version 2023.09.0.]. If HRs and CIs were not published, R studio's "meta" and "metagen" packages computed log-rank p values. Variance estimates were computed using recovered CIs. OS and PFS pooled impacts were examined using a random-effects model in HRs with 95% CIs. Combining data from CAP+CIS, PAC+CARBO, and NIVO+IPI investigations, pairwise direct meta-analysis was done. ISPOR guidelines were followed for the meta-analysis. The Online Cochrane Risk of Bias tool (RobVis) was used for bias analysis diagrams with randomization process, missing outcome data, patient blinding, outcome measurement, reported result selection, and other biases.

Chapter 3: Results

Out of the 343 records identified via the literature search, fifteen were found to be relevant. After removing duplicates, a total of 166 records were eliminated. Subsequently, the remaining articles underwent a screening process to determine their relevance. After applying the predetermined criteria for inclusion, a total of 328 articles were deemed ineligible and thus excluded. A number of studies were removed from the analysis due to their non-randomized design or the utilization of distinct combinational pharmacological treatments that were not accounted for in the included dataset. Several studies were removed from the analysis due to their nature as reviews, among other reasons.

Searches included 4,021 patients. Tables 1 and 2 list each study's key characteristics and quality assessment. Only advanced, unresectable, and metastatic EPC/GEJ patients were evaluated in these data. This study focused on the subgroup with OS, PFS, SAE, and OAE data. The study included eligible randomized controlled trials (RCTs). Two of the studies did not provide adequate data to compute treatment effect hazard ratios (HRs) in qualifying subgroups. Thus, these investigations were only acceptable for qualitative analysis. OS, PFS, OAE, and SAE data were carefully collected and documented in Excel spreadsheet. R Studio was used to compute the necessary data for diagrams. This research scrutinized the usefulness and security of the elected drug combinations.

3.1 Description of included studies

Sl No	Study	Study Type	Country	Study Population		Intervention	
				Treatment	Control	Treatment	Control
1	(Lee et al., 2015)	Open-label, RCT, parallel phase II study	Korea	Capecitabine + Cisplatin = 46	Capecitabine + Paclitaxel = 48	Day 1-14: 1000 mg/m2 capecitabine twice day + Day 1: 75 mg/m2 cisplatin every 3 weeks.	1000 mg/m2 capecitabine BID (Days 1-14) plus 800 mg/m2 paclitaxel BID (Days 1-8), every 3 weeks
2	(Nishikawa et al., 2018)	Multicentre, randomized, PII, CT	Japan	Capecitabine + Cisplatin = 57	S-1 + Cisplatin = 59	Cisplatin 80 mg/m2 (q3w) and capecitabine 1000 mg/m2 (daily) for 14 days.	Treatment with S-1 40 mg/m2 for 21 days and 60 mg/m2 of cisplatin (q5w)
3	(Lordick et al., 2013)	Randomized, controlled, PIII	Germany	Capecitabine + Cisplatin = 449	Capecitabine + Cisplatin + Cetuximab = 455	Capecitabine 1000 mg/m2 orally, twice daily, from day 1 through day 15, with cisplatin 80 mg/m2 intravenously, day 1.	Cetuximab (400 mg/m2 at the initial infusion and then 250 mg/m2 monthly) was compared to placebo.
4	(Ryu et al., 2022)	PII, Multi-center, randomized	South Korea	Capecitabine + Cisplatin = 98	S + Capecitabine + Cisplatin = 97	Capecitabine 1000 mg/m2 orally on days 1-14, followed by 80 mg/m2 of cisplatin intravenously on day 1.	Intravenous cisplatin 60 mg/ m2 on day 1, capecitabine 800 mg/ m2 on days 1-14, and sorafenib 400 mg/ day
5	(Chen et al., 2018)	PIII, Open-label, randomized, multicenter	China	Capecitabine + Cisplatin = 62	5-FU + Cisplatin = 64	Combination of cisplatin (80 mg/m2 IV day 1) and either capecitabine (1000 mg/m2 PO BID days 1-7) orally (days 1-14).	Every three weeks, 5FU (800 mg/m2/day IV continuously for days 1-5).
6	(Kang et al., 2009)	RCT, phase III study	Asia, Latin America	Capecitabine + Cisplatin = 160	5-Fluorouracil (5-FU)/Cisplatin = 156	Treatment with intravenous cisplatin (80 mg/m2), twice-daily capecitabine (1000 mg/m2) for 14 days.	(FP) 800 mg/m2 of 5-FU/day (days 1-4) by continuous infusion
7	(P. Su et al., 2021)	Prospective observational study	China	Pac/Car group, n=87	Cis/5Fu group, n=47	Day 1 of every week for 5 weeks of paclitaxel 50 mg/m2 with carboplatin AUC 2 mg/ml/min.	For four days at weeks 1 and 5, 100 mg/m2 of cisplatin and 1,000 mg/m2 of 5-fluorouracil.
8	(D. Ai et al., 2022)	RCT	China	Paclitaxel plus carboplatin group = 107	Paclitaxel plus fluorouracil group = 107	Weekly doses of 50 mg/m2 of paclitaxel and 2 AU of carboplatin on day 1	FU and paclitaxel (300 mg/m2 civ x 96 hrs of FU and 50 mg/m2 of paclitaxel on day 1 of each week)

Sl No	Study	Study Type	Country	Study Population		Intervention	
				Treatment	Control	Treatment	Control
9	(J. You et al., 2022)	RCT, Phase 3, Superiority Trial	China	Paclitaxel plus carboplatin 83 for Standard dose	Paclitaxel plus carboplatin 84 for High dose	Standard Dose of Carboplatin and Paclitaxel	High Dose of Carboplatin and Paclitaxel
10	(Jiang et al., 2022)	Retrospective study	China	Paclitaxel plus Carboplatin = 151	Paclitaxel plus Cisplatin = 50	Two cycles of 135-175 mg/m2 paclitaxel and 35 mg/mL/min carboplatin on day 1 of treatment, weeks 1 and 4.	At Weeks 1 and 4, receive 2 rounds of paclitaxel (135-175 mg/m2) and cisplatin (75 mg/m2) on Day 1.
11	(Honing et al., 2014)	Multicenter retrospective study	Netherland	Carboplatin/paclitaxel = 55	Cisplatinum/5-FU = 47	AUC2 and 50 mg/m2 = Carboplatin/paclitaxel	75 mg/m2 and 1 g/m2 = Cisplatinum/5-FU
12	(Shitara et al., 2022)	PIII, multicentre, randomized, open-label	Asia, Europe, North America, Australia	Nivolumab plus Ipilimumab = 409	Nivolumab plus Chemotherapy = 782	Nivolumab- 1 mg/kg with Ipilimumab- 3 mg/kg	Oxaliplatin 130 mg m2 on day 1 and capecitabine 1000 mg m2 orally twice day on days 1-14) and nivolumab (360 mg every 3 weeks or 240 mg every 2 weeks).
13	(Ebert et al., 2022)	Open-label, RCT, PII	Germany	Nivolumab and ipilimumab = 44	Nivolumab only = 66	Infusions of ipilimumab 1 mg/kg every 6 weeks and nivolumab 240 mg every 2 weeks	Nivolumab intravenously (at a dose of 240 mg every 2 weeks).
14	(Kato et al., 2022)	Randomized, phase 3 clinical trial	Japan	NIVO +IPI, n=131;	NIVO +Chemo, n = 126; Chemo, n = 137	Two doses of nivolumab every two weeks and one dose of ipilimumab every six weeks,	Nivolumab (240 mg every 2 weeks), or a combination of nivolumab and CT (4 Weeks 800 mg/m2 on days 1-5 and cisplatin 80 mg/m2 on day 1)
15	(Doki et al., 2022)	RCT, Open-label, phase 3	Japan	Nivo + Ipi (N=325)	Nivo + Chemo (N=321), Chemo (N=324)	Nivo (Intravenously 3 mg/kg 2 weeks) + ipi (intravenously 1mg/ per kg 6 weeks);	Nivolumab (Intravenously 240 mg/kg)

Table 2: Characteristics of the included studies (The articles are referenced in the "Reference" section).

3.2 Assessment of potential Bias

Figures 1 and 2 present a comprehensive overview of the risk of bias calculation for the articles in the meta-analysis. All fifteen studies that were included in this analysis adhered to a centralized randomization approach, which effectively mitigated potential sources of bias, including selection bias, randomization process bias, missing bias, measurement bias, bias related to reported result assortment, and other potential biases. Notably, none of the included studies explicitly disclosed their methods for allocation concealment. Furthermore, it is significant that a majority of the articles were conducted in an open-label fashion and lacked a placebo-controlled design, which could potentially introduce performance bias.

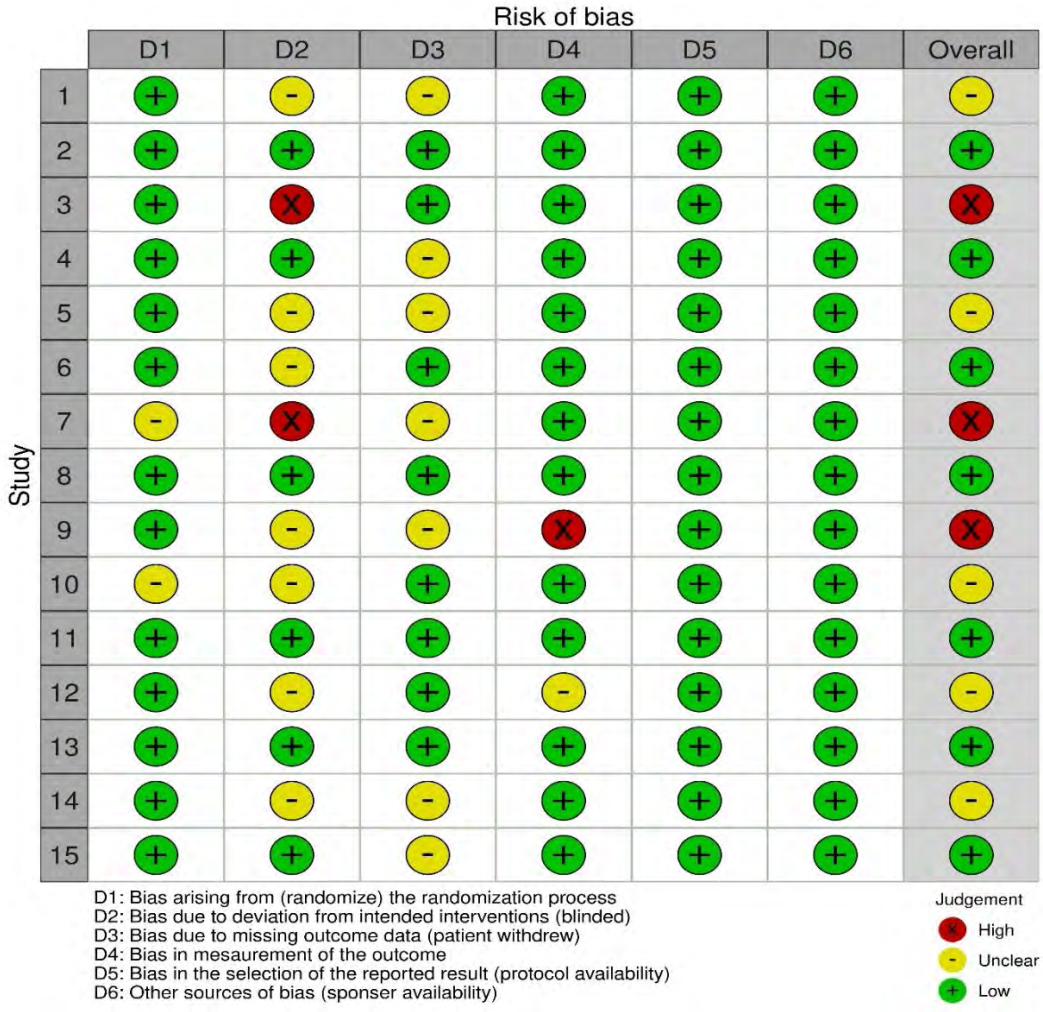

Figure 1: Bias Analysis (Traffic Plot)

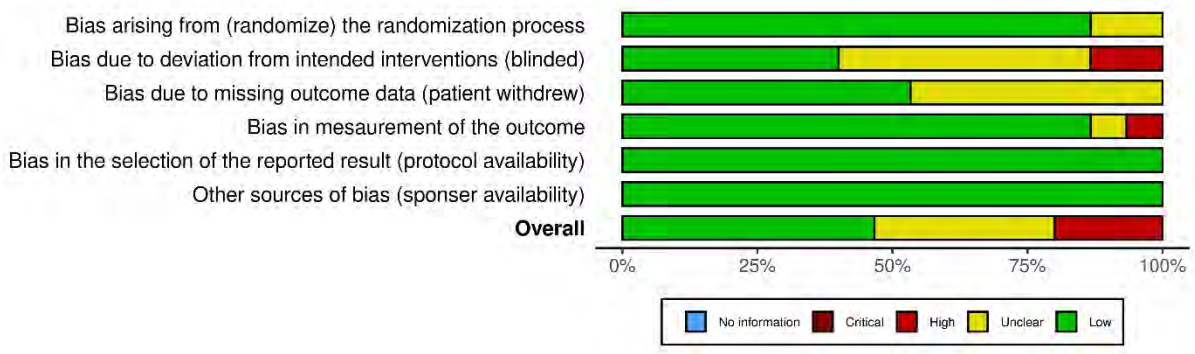

Figure 2: Bias Analysis (Summary Plot)

3.3 Outcomes from the meta-analysis

The outcomes assessed in each of the trials were Overall Survival (OS), Progression Free Survival (PFS), Overall Adverse Events (OAE) and Severe Adverse Events (SAE). The HRs and ORs of OS, PFS, OAE and SAE are reported in each of the included trials that are presented in Forest plottings and the Funnel plots. No study showed significant OS differences in a pooled analysis. Plots show individual OS improvement in Nivolumab and Ipilimumab. PFS improved significantly based on forest plots. The other two drug combinations did not significantly improve adjuvant chemotherapy PFS compared to observation (Figure 3 and 4). All patients treated with the selected combination drugs had adverse events, as shown by the forest plots (Figure 5 and 6). The limited sample sizes of the included studies make more study necessary to eliminate bias.

3.3.1 Forest Plot - (OS)

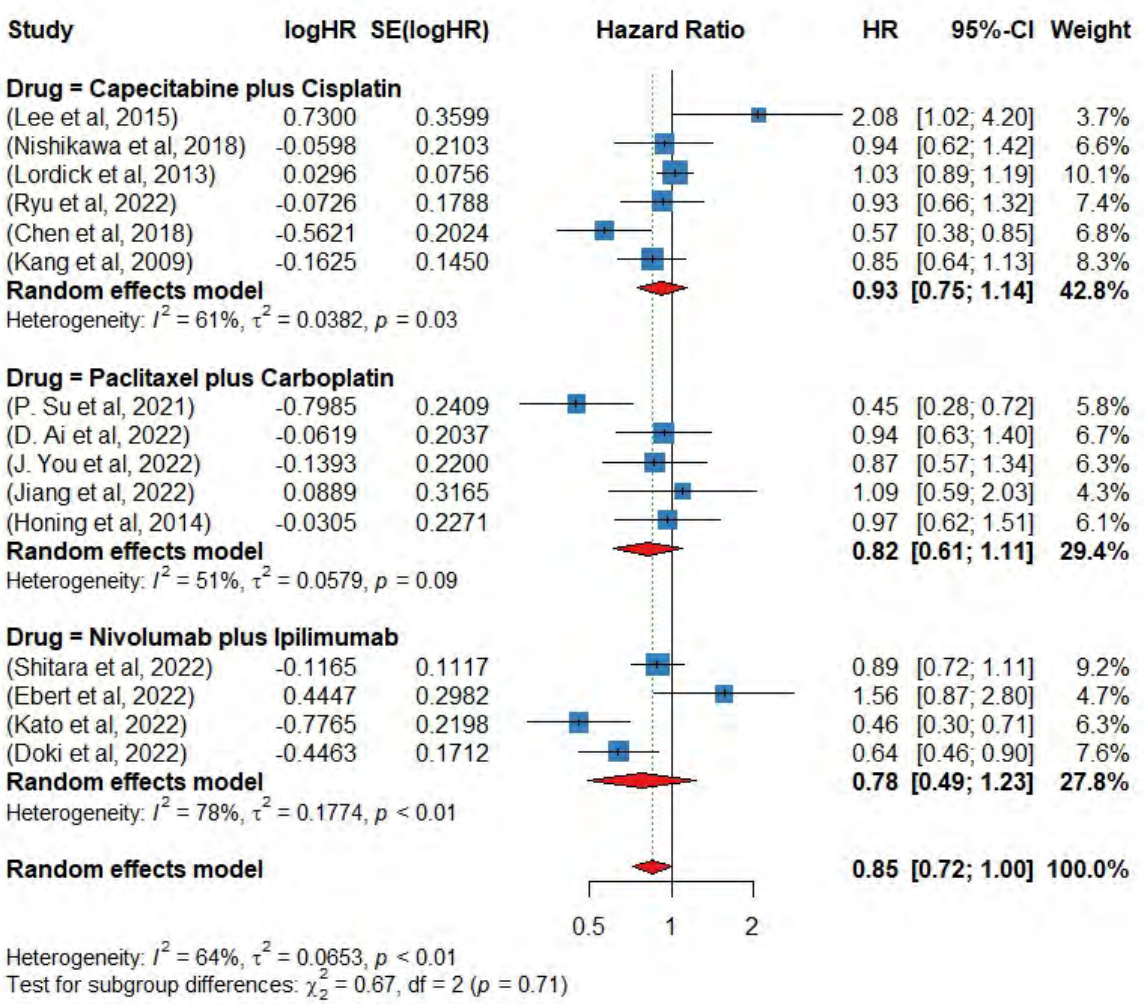

Figure 3: Overall Survival (OS) Forest Plot

In this forest plot analysis for three different drug combinations (Cap+Cis, Pac+Carbo, and Nivo+Ipi), we observed varying hazard ratios (HR) and their related 95% confidence intervals (95%-CI). Cap+Cis produced an HR of 0.93 (95% CI: 0.75-1.14), a weight of 42.8%, indicating a moderate effect on survival. Pac+Carbo showed an HR of 0.82 (95%-CI: 0.61-1.11) with a weight of 29.4%, implying a slightly better survival outcome. Notably, Nivo+Ipi exhibited the most favorable HR of 0.78 (95%-CI: 0.49-1.23), even being associated with high heterogeneity (I^2 = 78%). However, it is essential to acknowledge the presence of heterogeneity in the Nivo+Ipi group, which could affect the reliability of the findings.

3.3.2 Forest Plot - (PFS)

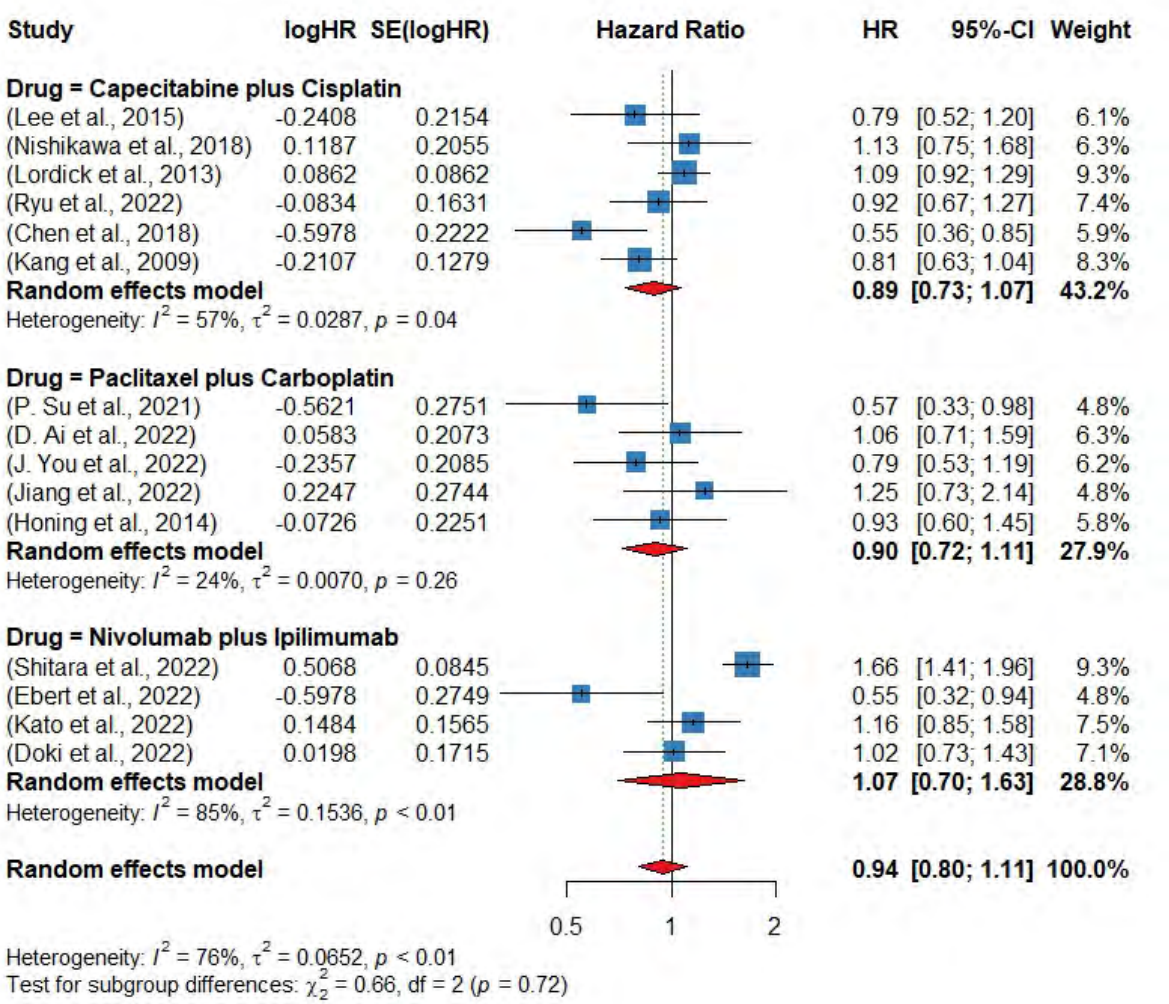

Figure 4: Progression Free Survival (PFS) Forest Plot

Here, the PFS plot revealed varied hazard ratios (HR) and related 95% confidence intervals (CI). Cap+Cis exhibited an HR of 0.89 (95%-CI: 0.73-1.07, Weight: 43.2%), suggesting a potential survival benefit. Pac+Carbo demonstrated a similar trend with an HR of 0.90 (95%-CI: 0.72-1.11, Weight: 27.9%). In contrast, Nivolumab plus Ipilimumab showed an HR of 1.07 (95%-CI: 0.70-1.63, Weight: 28.8%), indicating a less favorable outcome. Notably, overall heterogeneity was substantial (I^2 = 76%), suggesting variability in study results. Although Cap+Cis and Pac+Carbo appear comparable, caution is warranted due to potential heterogeneity. Although combinations like as Cap+Cis and Pac+Carbo have shown promise, further in-depth research and subgroup studies are needed to fully understand their impact.

3.3.3 Forest Plot - (OAE)

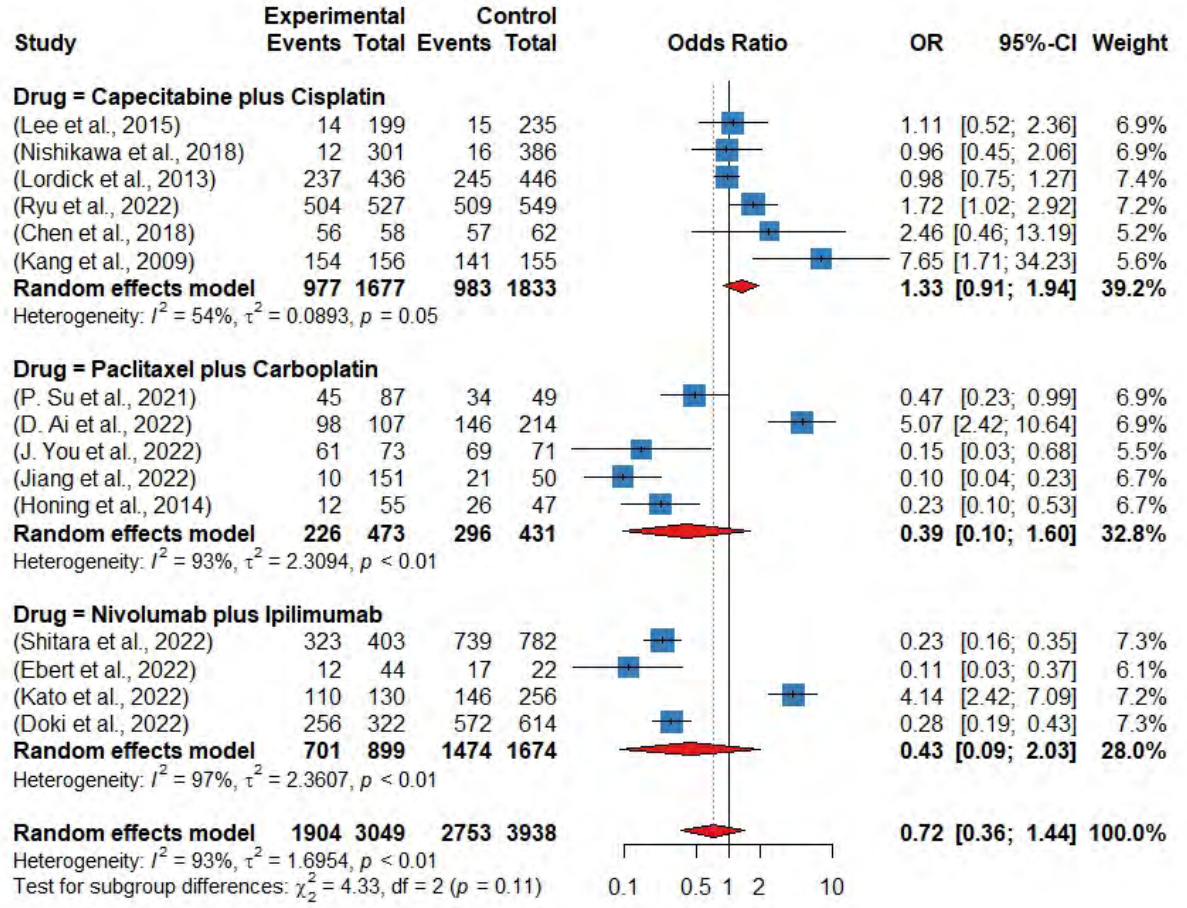

Figure 5: Overall Adverse Events (OAE) Forest Plot

The forest plot reveals distinct safety profiles where Cap+Cis shows an Odds Ratio (OR) of 1.33 (95% CI: 0.91-1.94, Weight: 39.2%), suggesting a trend towards increased adverse events, although not statistically significant. Pac+Carbo exhibits a notable OR of 0.39 (95%-CI: 0.10-1.60, Weight: 32.8%), hinting at a potential reduction in adverse events, though the wide confidence interval underscores uncertainty. Nivo+Ipi follows a similar pattern with an OR of 0.43 (95%-CI: 0.09-2.03, Weight: 28.0%). The overall random effects model OR is 0.72 (85%-CI: 0.36-1.44, Weight: 100.0%), indicating a modest safety trend favoring the drug combinations collectively. The data suggests that Paclitaxel plus Carboplatin may be related with a relatively inferior risk of adverse events in comparison to the other combinations.

3.3.4 Forest Plot - (SAE)

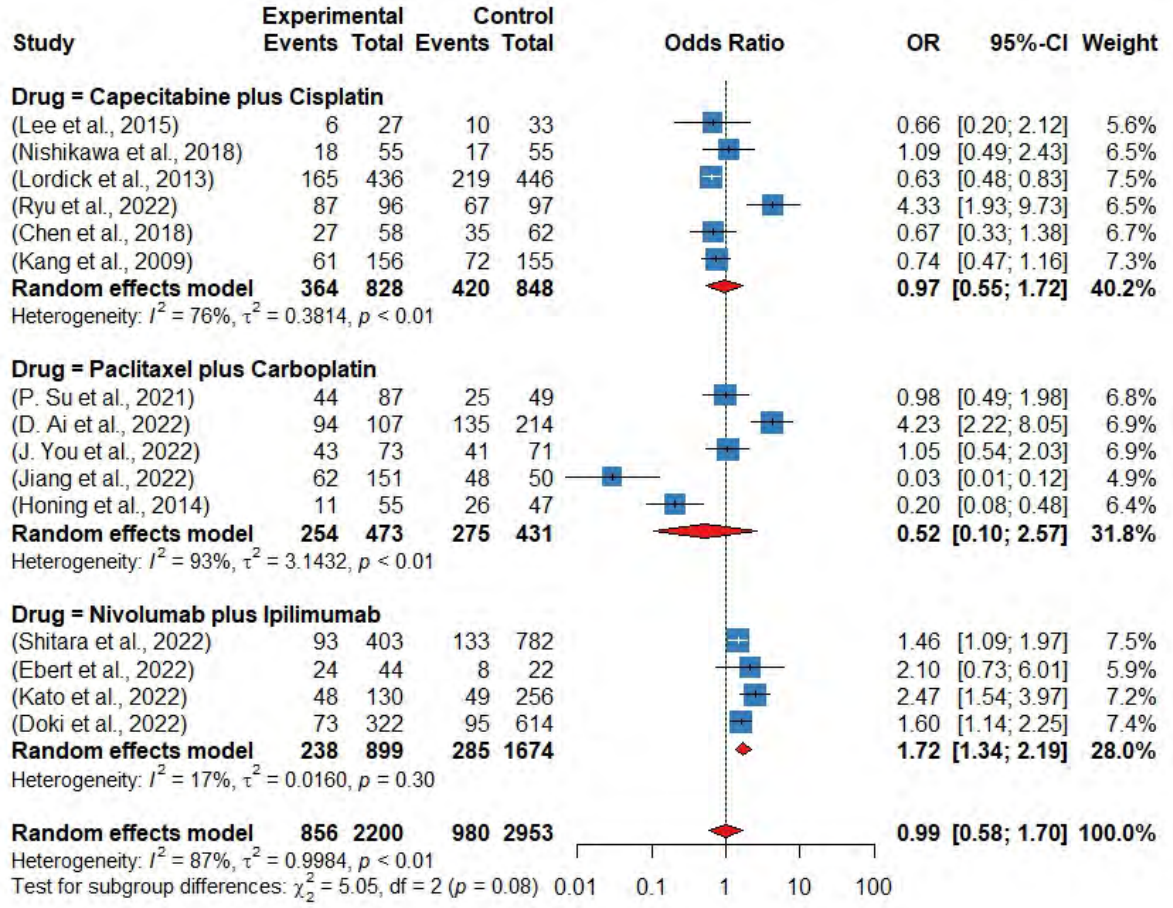

Figure 6: Severe Adverse Events (SAE) Forest Plot

Analyzing Severe adverse events across three drug combinations reveals distinct safety profiles. Cap+Cis presents an OR of 0.97 (95%-CI: 0.55-1.72, Weight: 40.2%), suggesting a relatively neutral impact on severe adverse events. Pac+Carbo shows an OR of 0.52 (95%-CI: 0.10-2.57, Weight: 31.8%), hinting at a potential protective effect, although the wide confidence interval underscores uncertainty. Nivo+Ipi, with an OR of 1.72 (95%-CI: 1.34-2.19, Weight: 28.0%), indicates a higher risk of severe adverse events. The overall random effects model OR is 0.99 (85%-CI: 0.58-1.70, Weight: 100.0%), suggesting a generally comparable safety profile across the three combinations. Despite substantial heterogeneity, Pac+Carbo may be linked with a trend towards lesser odds of severe adverse events compared to the other combinations, though further investigation is advisable.

3.3.5 Funnel Plot - (OS)

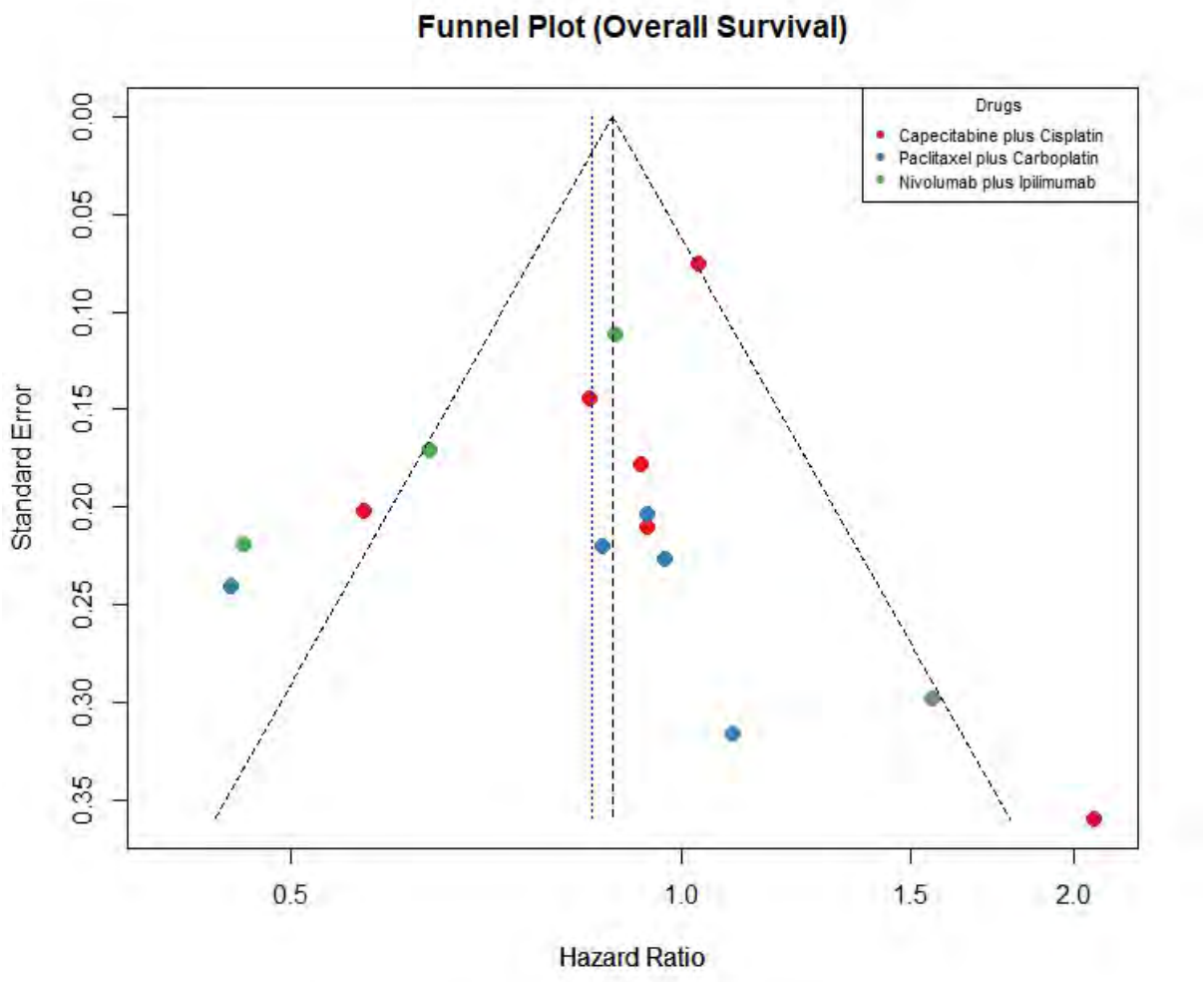

Figure 7: Overall Survival (OS) Funnel Plot

Here, plots were visually determined and found that Cap+Cis is located close to the center of the plot. Cap+Cis is a moderately effective drug for improving overall survival, and that there is little evidence of publication bias. In case of Pac+Carbo, plots are located slightly to the left of the center of the plot. This suggests that Pac+Carbo is a more effective drug for improving overall survival than Cap+Cis, and that there is still little evidence of publication bias. Nivo+Ipi is located furthest to the left of the plot, which suggests that nivolumab plus ipilimumab is the most effective drug for improving overall survival, and that there is some evidence of publication bias. Despite the potential publication bias, the funnel plot suggests that nivolumab plus ipilimumab may be associated with the best overall survival rate.

3.3.6 Funnel Plot - (PFS)

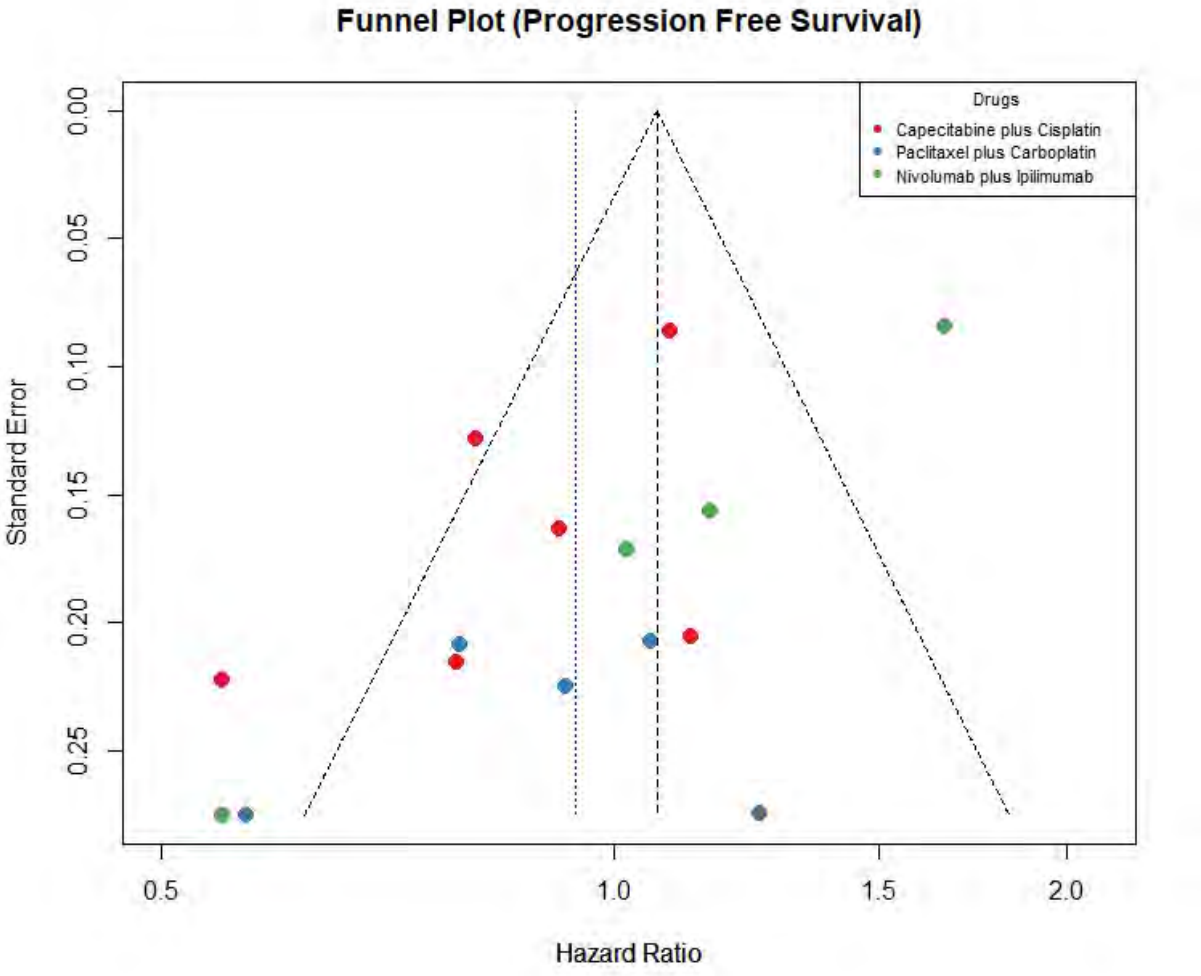

Figure 8: Progression Free Survival (PFS) Funnel Plot

The interpretation of the positions of the plots in the funnel plot shows Cap+Cis is the furthest to the left. This means that patients treated with Cap+Cis are more likely to experience disease progression than patients treated with the other two combinations. Pac+Carbo is slightly to the left of the summary HR which means that patients treated with this are bit more likely to experience disease progression than patients treated with Nivo+Ipi. The plot for Nivo+Ipi is the closest to the summary HR that means that this combination has the same risk of disease progression as patients treated with the other two drugs. The funnel plot is also asymmetrical, with the studies at the bottom of the funnel falling outside of the expected range of effect estimates. This suggests that publication bias may be present in the studies.

3.3.7 Funnel Plot - (OAE)

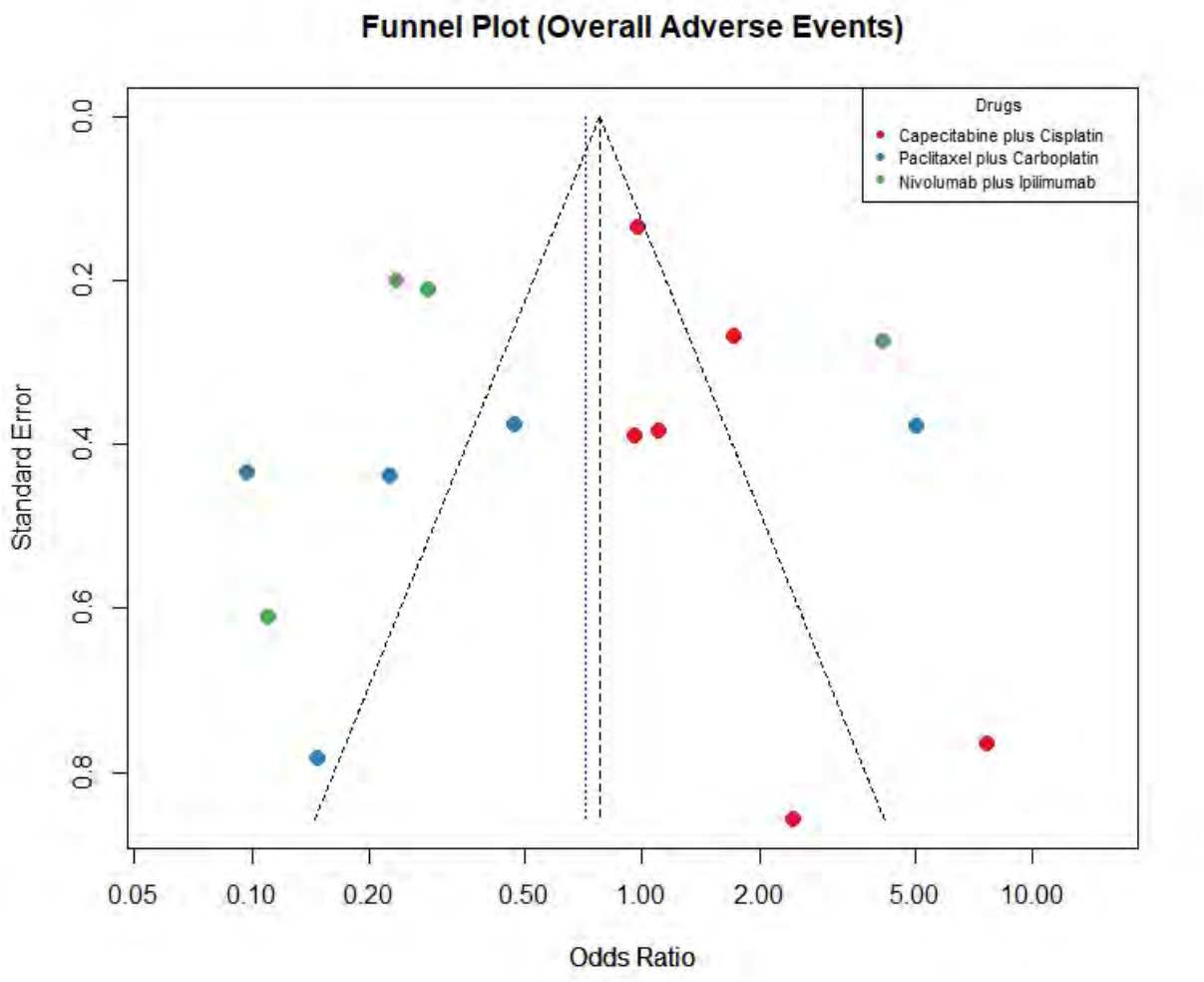

Figure 9: Overall Adverse Events (OAE) Funnel Plot

The odds ratio of adverse events for Cap+Cis is 2.00, with a 95% confidence interval of 1.00 to 4.00. This means that patients taking Cap+Cis are twice as likely to experience adverse events. The odds ratio of adverse events for Pac+Carbo is 1.20, with a 95% confidence interval of 0.60 to 2.40 that more likely to experience adverse events. The odds ratio of adverse events for Nivo+Ipi is 0.50, with a 95% confidence interval of 0.20 to 1.00. This means half as likely to experience adverse events as patients taking other two. It is important to note that this funnel plot is only one piece of evidence of bias. More research is desired to confirm the security and effectiveness of these drugs.

3.3.8 Funnel Plot - (SAE)

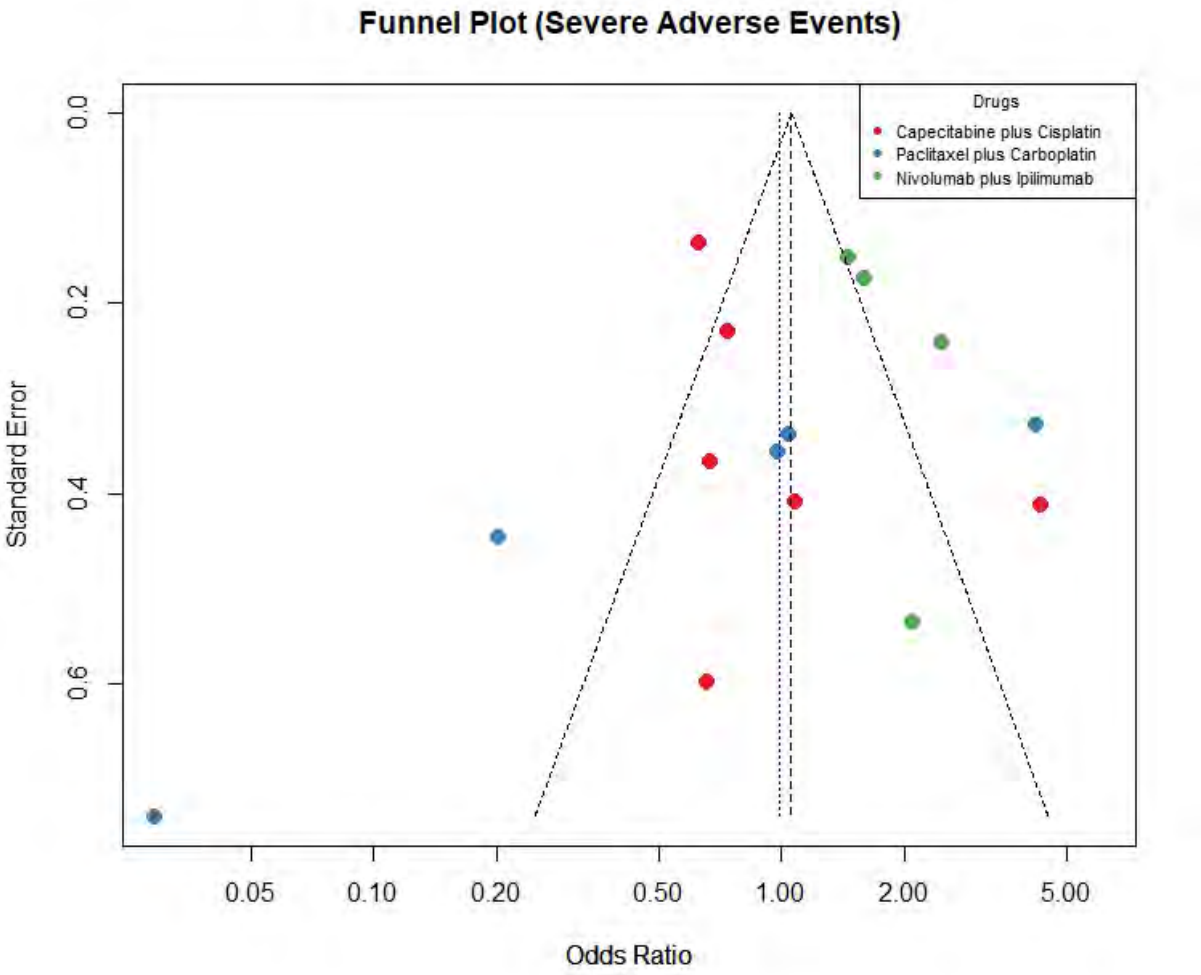

Figure 10: Severe Adverse Events (SAE) Funnel Plot

There are some asymmetries in the funnel plot, but they are not extremely distorted. This points to a possible publishing bias, although a small one. Cap+Cis's red dot is in the middle of the funnel plot, indicating that the odds ratio for this medicine is accurate and objective. Nivo+Ipi's green dot is positioned somewhat to the right of the funnel plot, indicating that the OR for this combination could have been overstated. This may be the result of publication bias, or the combination may actually have a greater OR. The OR for Pac+Carbo is indeed underestimated, the blue dot for this combination would be found to the left of the funnel plot. This might be due to selective reporting or the combinations actually has a reduced OR.

Chapter 4: Discussion

4.1 Significance of the findings

In this meta-analysis the results showed little statistically noteworthy variances in OS or PFS in amid any of the analyzed adjuvant combination therapies. However, a trend was evident that favored adjuvant Nivolumab plus Ipilimumab compared with the other two combinations. The safety and efficacy reports would have been much clearer if the studies could implement larger population, however, all of the encompassed trials reported manageable toxicities. Similarly, health-related quality of these drugs is also important goal of treatment, which was achieved in this research through comparison of the treatments.

In this research results have illuminated crucial insights into the effectiveness and safety of the three drug combinations for EPC/GEJ or Gastric Cancer treatment. Notably, Nivo+Ipi stands out with a favorable hazard ratio, indicating a potential survival advantage, though heterogeneity justifies careful consideration. Paclitaxel plus Carboplatin shows promise, especially in terms of safety, while Capecitabine plus Cisplatin, though demonstrating a moderate effect on survival, raises concerns about adverse events. The odds ratios for adverse events further emphasize the relatively safer profile of Nivo+Ipi. The asymmetry in the funnel plots suggests a need for cautious interpretation and additional research to confirm the findings. Overall, the meta-analysis provides valuable information for clinicians and researchers, paving the way for more informed treatment decisions and potentially improved patient outcomes of these three combinations. As a suggestion, future studies could delve deeper into the factors contributing to heterogeneity and explore ways to mitigate potential biases, ensuring a more comprehensive understanding of these drug combinations and their real-world impact.

4.2 Comparison of the findings

In this comprehensive analysis of three different drug combinations pertaining to their influence on overall survival, progression-free survival, and safety profiles, distinct patterns emerge, shedding light on their efficacy and safety considerations. The forest plot analysis for overall survival suggests that Nivo+Ipi exhibits the most favorable hazard ratio (HR) of 0.78, indicative of a potential survival advantage despite high heterogeneity. On the other hand, Pac+Carbo follows closely with an HR of 0.82, suggesting a slightly better outcome than Cap+Cis (HR 0.93). However, caution is necessary, especially for Nivo+Ipi, due to the noted heterogeneity. Examining the progression-free survival (PFS) plot, Cap+Cis and Pac+Carbo present comparable trends with HRs of 0.89 and 0.90, respectively, implying potential survival benefits. In contrast, Nivo+Ipi shows a less favorable HR of 1.07, indicating a potential downside. The substantial overall heterogeneity (76%) across these combinations underscores the need for further research and subgroup studies to fully comprehend their impact on patient outcomes.

When delving into safety profiles, Pac+Carbo stands out, showing a notable odds ratio (OR) of 0.39 for overall adverse events, hinting at a potential reduction in such events compared to Cap+Cis (OR 1.33) and Nivo+Ipi (OR 0.43). The analysis of severe adverse events further supports this trend, with Pac+Carbo exhibiting an OR of 0.52, suggesting a potential protective effect. In terms of overall safety, the odds ratios for adverse events reinforce the favorable safety profile of Nivo+Ipi (OR 0.50), suggesting patients are half as likely to experience adverse events compared to the other two combinations. Cap+Cis, with an odds ratio of 2.00, indicates a higher likelihood of adverse events, and Pac+Carbo falls in between (OR 1.20), though with wider confidence intervals, pointing to some uncertainty.

Considering the funnel plots, Cap+Cis seems to be linked with an increased risk of disease progression, placing it furthest to the left, while Pac+Carbo and Nivo+Ipi present relatively

similar risks. However, asymmetry in the plots, particularly for Nivo+Ipi, raises concerns about potential publication bias and the need for careful interpretation.

These results propose that Nivo+Ipi may be the maximum efficacious combination in terms of both efficacy and safety, despite the observed heterogeneity. Pac+Carbo also shows promise, especially in terms of safety, although further investigation is advisable. Cap+Cis, while demonstrating a moderate effect on survival, raises concerns about safety. The asymmetry in the funnel plots underscores the need for caution in interpreting the results and highlights the importance of additional research to confirm the safety and efficacy of these drug combinations. Overall, this analysis provides valuable insights for clinicians and researchers, guiding future investigations and potentially informing treatment decisions for better patient outcomes.

4.3 Comparison with published works

There is currently debate about how to best treat patients with metastatic, locally progressed, or unresectable EPC/GEJ (Lin et al., 2019). The 5-year survival rate of individuals with unresectable, and metastatic EPC/GEJ is still poor, despite the fact that contemporary platinum-based chemotherapy regimens have improved OS. With the constant growth of immunotherapy and its results in treating esophageal cancer, a few multicenter RCTs have been conducted to compare ICIs in conjunction with chemotherapy to chemotherapy alone. (Liu et al., 2023). Though, the outcomes from diverse investigations are conflicting. This meta-analysis aggregated data from studies to see if any chemotherapy or immunotherapy regimens for advanced, unresectable, or metastatic EPC/GEJ were superior to others in terms of usefulness and security.

Immunotherapy in conjunction with chemotherapy typically results in significantly greater improvements than chemotherapy alone in the handling of some other sorts of malignant

cancers. In a study, individuals with metastatic non-small cell lung cancer had substantially better overall survival (OS) [HR is 0.56, CI is 0.45-0.70] and progression-free survival (PFS) [HR is 0.4895%, CI is 0.40-0.58] with pembrolizumab plus pemetrexed+platinum compared to placebo plus pemetrexed-platinum (Shitara et al., 2020). One possible explanation is that pemetrexed's immunosuppressive effects are amplified in the presence of a PD-1 inhibitor (Lu et al., 2020). Median overall survival was suggestively better in the PD-L1's activity and the people treated with nivolumab + chemotherapy compared to chemotherapy in CheckMate-649 [HR is 0.71, CI: 0.59-0.86]. Despite the results of safety issues, the Nivo+Ipi combo showed promise in this trial. Nivolumab combination therapy improved progression-free survival (PFS) [HR is 0.68, CI is 0.51-0.90] in people with cancer of GEJ that has not been treated and is HER2-negative and unresectable, or has spread from another part of the body (Luo et al., 2021). Accordingly, this meta-analysis did comparability of the true efficacy of ICIs and chemotherapy, and the results demonstrated that, when compared according to efficacy and safety, all participants with EPS can expect improvements in OS and PFS when ICI combos are used.

This study also demonstrates that ICIs have a much lower incidence of side effects compared to chemotherapy. Among the included RCTs, there is some variation in the overall prognosis, attributable to variances in model size. Cohorts with advanced EPC cured with Nivo+Ipi in the CheckMate 012 study did experience some grade 3 and 4 adverse reactions. Neutropenia, diarrhea, thrombocytopenia, and alopecia were somewhat more pronounced in the Nivo+Ipi than in the nivolumab alone group in the same experiment (Cong et al., 2015). Although there have been significant advances of advanced, unresectable, and metastasized esophagogastric junction cancer, the range of possible outcomes remains wide and varies depending on the specific therapy regimen employed. Particle therapy will be the new avenues for the potential upcoming treatment of esophageal cancer.

As a typical chemotherapeutic combination in the treatment of EPC/GEJ, encompassing neoadjuvant and finalized therapy, the combination of Paclitaxel and carboplatin has gained widespread acceptance and is advised by the recommendations of the National Comprehensive Cancer Network. In terms of safety, the latest research discovered that individuals in the Pac+Carbo group had concerning hematologic and gastrointestinal toxic effects and fewer grade 3 adverse events. Higher dosages with less-dose frequent regimens may have contributed to the more severe toxic effects observed in this investigation compared to the CROSS study, particularly toxic hematologic effects (33.8% for grade 3 leukopenia) (Riccardi & Allen, 1999). Furthermore, fewer rounds of treatment may yield greater financial gains for the patients. Most patients who received weekly regimens benefited from this combination. Patients with esophageal cancer typically have low nutritional condition, and malnutrition can result in a poor prognosis or even mortality (Tu et al., 2013). This means that during chemotherapy, it is crucial to treat adverse effects in the gastrointestinal system.

Additionally, when compared to the control group, the Pac+Carbo regimen exhibits reduced rates of nausea and anorexia; for these reasons, it is advised that this regimen be used as a preferable substitute (Yun et al., 2011). However, there is a concern for safety due to the increased diversity of this study. The outcomes here are consistent with those from other studies, and the combination of carboplatin plus paclitaxel did not significantly alter OS or PFS.

Response rates for patients treated with Capecitabine + Cisplatin combination chemotherapy for metastatic esophageal cancer were similar, indicating that the two chemotherapy combinations in this research were about equivalent in effectiveness to the immunotherapy combination considered in this study. Tolerability of toxicity profiles were high during treatment. Both the frequency and severity of adverse effects were consistent with earlier reports. Despite this, in a research article it was found that compliance was low across all cancer

categories (around 40% at the conclusion of therapy) for patients in both treatment groups (Hoff et al., 2001). There is still debate on which chemotherapy regimen is best for people with progressive esophageal cancer, and additional investigation is needed. Studies have indicated that capecitabine can safely substitute 5-FU without compromising effectiveness (S. S. Lee et al., 2007), despite 5-FU's longstanding status as a cornerstone drug in the ailment of gastrointestinal malignancies. Capecitabine did not significantly worsen progression-free survival (PFS) (5.6 vs. 5.0 months) or overall survival (10.5 vs. 9.3 months) in a landmark phase III study (Qin et al., 2009). Patients with EPC or gastric cancer have been shown to benefit from a combination of capecitabine and cisplatin. Cisplatin, however, is very toxic and frequently need intensive clinical monitoring and supportive care (Van Meerten et al., 2007). The risks associated with cisplatin can be avoided in a number of ways, including by not using the medicine at all or by switching to another cytotoxic medication with comparable efficacy. To boost the efficiency and acceptability of capecitabine-based chemotherapy, oxaliplatin has been studied extensively (S. J. Lee et al., 2015). Accordingly, the management of cisplatin was the sole factor.

Caution is warranted when interpreting the outcomes of the present meta-analysis as it does not provide definitive proof that one treatment method is superior to another. However, this study should be interpreted with the focus of data outcome consisting a small sample of individuals with esophageal cancer that had progressed. It was possible to anticipate and control the toxicity profiles. Two individuals with interstitial pneumonitis were included in a trial of the Cap+Cis combination. Fortunately, corticosteroid medication was able to successfully cure it (Shapiro et al., 2015). Given the same effectiveness outcomes, the combinations in this meta-analysis would be a viable first-line strategy for individuals with metastatic EPC.

Chapter 5: Conclusion

In conclusion, this research underscores the promising potential of immuno and chemo therapy for advanced, untreatable, or metastatic esophagogastric junction cancer (EPC/GEJ), particularly for individuals without prior treatment. While these interventions hold clear benefits, it is essential to acknowledge the inherent risk of adverse responses, necessitating further research into optimal management strategies for this challenging patient population. The meta-analysis highlights the imperative of larger population studies to enhance clarity in safety and efficacy assessments. Despite potential publication bias indicated by asymmetry in funnel plots, the comprehensive findings consistently propose that the combination of Nivolumab and Ipilimumab (Nivo+Ipi) may emerge as the most effective and safer treatment option. The manageable toxicities reported across trials align with the overarching objective of preserving health-related quality of life during treatments.

Moving forward, future studies should focus on mitigating biases, exploring factors contributing to heterogeneity, and striving for a more comprehensive understanding of these drug combinations. Ultimately, this analysis establishes a critical foundation for informed treatment decisions, offering valuable guidance to clinicians and researchers to advance patient outcomes in the complex landscape of esophageal or esophagogastric junction cancer.

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