“Clinical Outcomes and Safety Comparison of Gemcitabine plus Cisplatin, Capecitabine Monotherapy, and Gemcitabine plus Oxaliplatin in the Management of Gallbladder Carcinoma: A Comprehensive Meta-Analysis”

By

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A thesis given to the School of Pharmacy in fractional fulfillment of the necessities for the degree of Bachelor of Pharmacy (Hons.)

School of Pharmacy
Brac University
February 2024

Declaration

The statement affirms the following assertions:

1. The submitted thesis represents solely my independent effort, crafted exclusively for my academic pursuit at Brac University.
2. The thesis abstains from incorporating any preexisting or externally authored material without appropriate acknowledgment through accurate and comprehensive referencing.
3. No portion of the thesis has been utilized or accredited towards any other academic qualification or certification from any institution or entity.
4. Recognition has been duly provided to all significant sources of support or guidance received during the thesis development process.

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Approval

The project titled “Clinical Outcomes and Safety Comparison of Gemcitabine plus Cisplatin, Capecitabine Monotherapy, and Gemcitabine plus Oxaliplatin in the Management of Gallbladder Carcinoma: A Comprehensive Meta-Analysis” submitted by Sanjida Rahman (ID: 18346027) of Summer, 2018 has been acknowledged reasonably meeting the requirements for the Bachelor of Pharmacy on February, 2024.

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Ethics Statement

This research does not comprise any experiments or trials conducted on humans or animals.

Abstract

Introduction: The utilization of chemotherapy treatment (CT) in the context of biliary tract cancers (BTC) remains a subject of considerable debate. To date, no comprehensive efficacy assessment has been conducted to directly compare the outcomes of chemotherapy (CT) in the patient population. It is worth noting that recent years have witnessed notable advancements in chemotherapy interventions for BTC. However, it is imperative to underscore that further research and investigation are necessary to comprehensively understand the full scope of treatment options and their relative effectiveness in addressing this challenging disease.

Method: We searched the databases of PubMed, Biomed, Scholarly, and The Cochrane Library to find published publications that were relevant. We selected RCTs with patients with BTC undergoing adjuvant chemotherapy for our systematic analysis, which covered publications from 2010 to 2022. Indirect comparisons of overall survival (OS), progression-free survival (PFS), severe adverse events (SAE), and overall adverse events (OAE) were conducted using meta-analysis methods. Different chemotherapy treatments were selected. We employed a random-effects model for aggregating the data.

Result: A total of 4395 individuals from 18 trials were examined, all of whom got the chemotherapy of our choosing. The findings of the indirect comparison showed that there was no discernible increase in overall survival for either Capecitabine plus Gemcitabine plus Oxaliplatin or Gemcitabine plus Cisplatin. The hazard ratios (hrs) for each combination were 1.69 [95% (CI): 1.17 to 2.44, 1.92 [95% (CI): 0.98 to 3.77, and 0.93 [95% (CI): 0.69 to 1.25], respectively. Likewise, there was no discernible increase in PFS among the three distinct medication categories under scrutiny. Despite this, gemcitabine + oxaliplatin continues to be more effective.

Conclusion: We did not find any statistically significant improvements in OS or PFS for any of the three medication groups in the current analysis. Because of its better effectiveness, gemcitabine + oxaliplatin can be regarded the standard of therapy in the adjuvant scenario until more prospective studies are completed.

Keywords: Biliary tract cancer, medical oncology, chemotherapy, clinical trials, targeted therapy; immunotherapy.

Dedication

To my family who are always ready to support me in every situation

Acknowledgement

In the beginning I want to thank Allah for granting me the asset and determination to finish this project. I am also appreciative of numerous individuals whose contributions were indispensable to the completion of this project.

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Table of Contents

List of Tables

List of Figures

List of Abbreviations

GBC	Gallbladder Cancer
OS	Overall Survival
PFS	Progression Free Survival
SAE	Severe Adverse Events
OAE	Overall Adverse Events
HR	Hazard Ratio
OR	Odds Ratio
CI	Confidence Interval
RCT	Randomized Controlled Trial
CT	Chemotherapy
RT	Radiotherapy

Chapter 1: Introduction

1.1 Background

In recent times, most prevalent and serious type of BTC (biliary tract cancer) is gallbladder cancer (GBC). However, only around 10 percent of individuals with GBC who have early-stage disease are thought to be good candidates for total surgical removal, which is the sole cure opportunity. Even after "curative" resection, recurrence is common among individuals. No proven adjuvant therapies exist for this condition. The prognosis for patients with GBC that is unresectable or have spread is dismal (Zhu et al., 2010). Unfortunately, the prevailing treatment approach for cancer patients involves surgical resection, a procedure successfully completed by only a minority of patients. The high fatality rate has continued for years as a result. Immunotherapy, targeted treatment, and delivery methods based on nanoparticles are just some of the therapeutic approaches that have been intensively innovated because of the development of innovative technological measures (e.g., transcriptomics, proteomics next-generation sequencing) to significantly sidestep the stale situation (Song et al., 2020). There are several potential drugs being studied for the treatment of Gallbladder cancer, including gemcitabine and cisplatin, which are commonly used in combination chemotherapy regimens. Additionally, targeted therapies such as ramucirumab and pembrolizumab are being investigated for their effectiveness in specific subsets of individuals with advanced Gallbladder cancer

1.2 Treatment of Gallbladder Cancer

A malignant tumor that starts in the gallbladder is called gallbladder cancer, and it is a very uncommon but deadly type of cancer. The little, pear-shaped organ called the gallbladder sits underneath the liver and is in charge of holding the bile that the liver produces. (Roa et al., 2022). Unfortunately, gallbladder cancer often goes undetected until it reaches advanced stages, making it difficult to treat. Its prevalence varies across different regions, with higher

rates reported in certain portions of the world, such as Central and Eastern Europe, South America, and Asia (Roa et al., 2022). Although the exact causes of gallbladder cancer remain unclear, factors such as gallstones, chronic inflammation, obesity, and genetic predisposition are believed to contribute to its development (Zhu et al., 2010). Early detection and prompt medical intervention are crucial in improving the prognosis for individuals affected by this challenging disease.

Among the 45 nations researched, the incidence of GBC dropped in 3 and climbed in 5 between 1980 and 2017; among women, the incidence decreased in 13 and increased in 4, globally 3. Twelve more nations than before had decreases in mortality rates; male mortality fell in eight of forty-four countries (18%) and female mortality fell in eighteen of forty-four (41%). Each subgroup has a unique pattern (Huang et al., 2021). According to US statistics, for instance, the rate of rise was 1.8% annually between 1999 and 2003 among people of African descent and among those younger than 45. Both males and female's death rates rose between 1980 and 2017 in Ecuador (2.3%), Germany (1.2%), the Netherlands (2.9%), and the United Kingdom (2.6%). In addition, male death rates appear to have risen between 2010 and 2016 in both Colombia and Canada (Rashighi & Harris, 2017).

Moreover, Gallbladder cancer in Bangladesh is a significant health concern, as the country experiences a relatively high prevalence of this malignancy. It is among the main reasons why people die from cancern among Bangladeshi adults. Several factors contribute to the increased incidence, including a high prevalence of gallstones, which are a known risk factor for gallbladder cancer. According to a study carried out in HBPS unit, BIRDEM Hospital, Dhaka, Twenty GBC patients were studied in a row for this investigation. After cholecystectomy, histopathology revealed cancer in the gall bladder in 3 individuals, or 15%. Curative resection was performed on 7 individuals (35%). Palliative care was provided to 13 patients (65%). There was a 5-year PFS rate of 35% in this trial. Curative radical resection (enmass resection or

bisegmentectomy following cholecystectomy) was performed on these stage Ib and II patients. Approximately 65% of individuals had a dismal prognosis (Alam et al., 2019).

1.3 Drugs for GBC

Based on the prevalence and severity of this disease several drug classes were chosen as the effective candidates to treat the malignancy as effectively as possible. In GBC, surgical operation is the only remedial option, however reappearance may occur even after a successful resection. Therefore, there is a lot of enthusiasm for including neoadjuvant or adjuvant therapy into the current typical mode of care for GBC treatment. In the neoadjuvant setting, NCCN recommends a number of chemotherapy regimens, despite the death of several patients. Combinations of gemcitabine with cisplatin, oxaliplatin, or capecitabine with oxaliplatin, or 5-fluorouracil (5-FU), are all examples (Okumura et al., 2021).

Among the effective drugs are 2 combination and 1 solo drug that were chosen for this paper. Gemcitabine and cisplatin have shown promising effectiveness in the handling of GBC. Gemcitabine functions as a nucleoside analogue, impeding DNA synthesis, whereas cisplatin is a platinum-based compound that triggers DNA damage. The combination of these drugs has demonstrated synergistic cytotoxic effects, resulting in improved overall survival rates and disease control (Azizi et al., 2021). Similar effect goes for another combination of drug with Gemcitabine plus Oxaliplatin.

Another drug with single therapeutic effect is Capecitabine which has shown effectiveness in the treatment of gallbladder cancer. It is an orally prodrug that the body breaks down into 5-fluorouracil (5-FU). 5-FU is a cytotoxic medicine that prevents the growth of cancer cells by interfering with DNA synthesis. Capecitabine offers convenience and improved tolerability compared to venous administration of 5-FU. Studies have demonstrated favorable response

rates and survival outcomes with capecitabine in gallbladder cancer patients, particularly in conjunction with other chemotherapy drugs (Kim et al., 2019)

1.4 Objectives and Aims

In order to compare the effectiveness of various chemotherapy regimens for patients with biliary tract tumors (BTC), a systematic analysis will be carried out, with an emphasis on progression-free survival (PFS) and overall survival (OS). The study's specific objectives are to evaluate the effectiveness of adjuvant chemotherapy regimens, such as Capecitabine plus Gemcitabine plus Oxaliplatin and Gemcitabine plus Cisplatin, and to ascertain whether these treatments differ significantly in terms of survival rates. In order to improve knowledge of treatment approaches for this difficult disease, the goal is to provide light on the relative efficacy of these chemotherapeutic alternatives in treating BTC.

Chapter 2: Process and Methodology

2.1 Inclusion and Exclusion Criteria

Reports by histology confirmed BTC patients encompasses individuals diagnosed with both intrahepatic and extrahepatic bile duct cancer, as well as gallbladder cancer who are undergoing adjuvant therapy or chemoradiation either before or after a total surgical resection (R0 or R1) were included if they were phase ii, iii randomized trials. Only trials containing the desired outcomes - OS, PFS, OAE, SAE, and numerous others - were allowed to proceed. (Table 1).

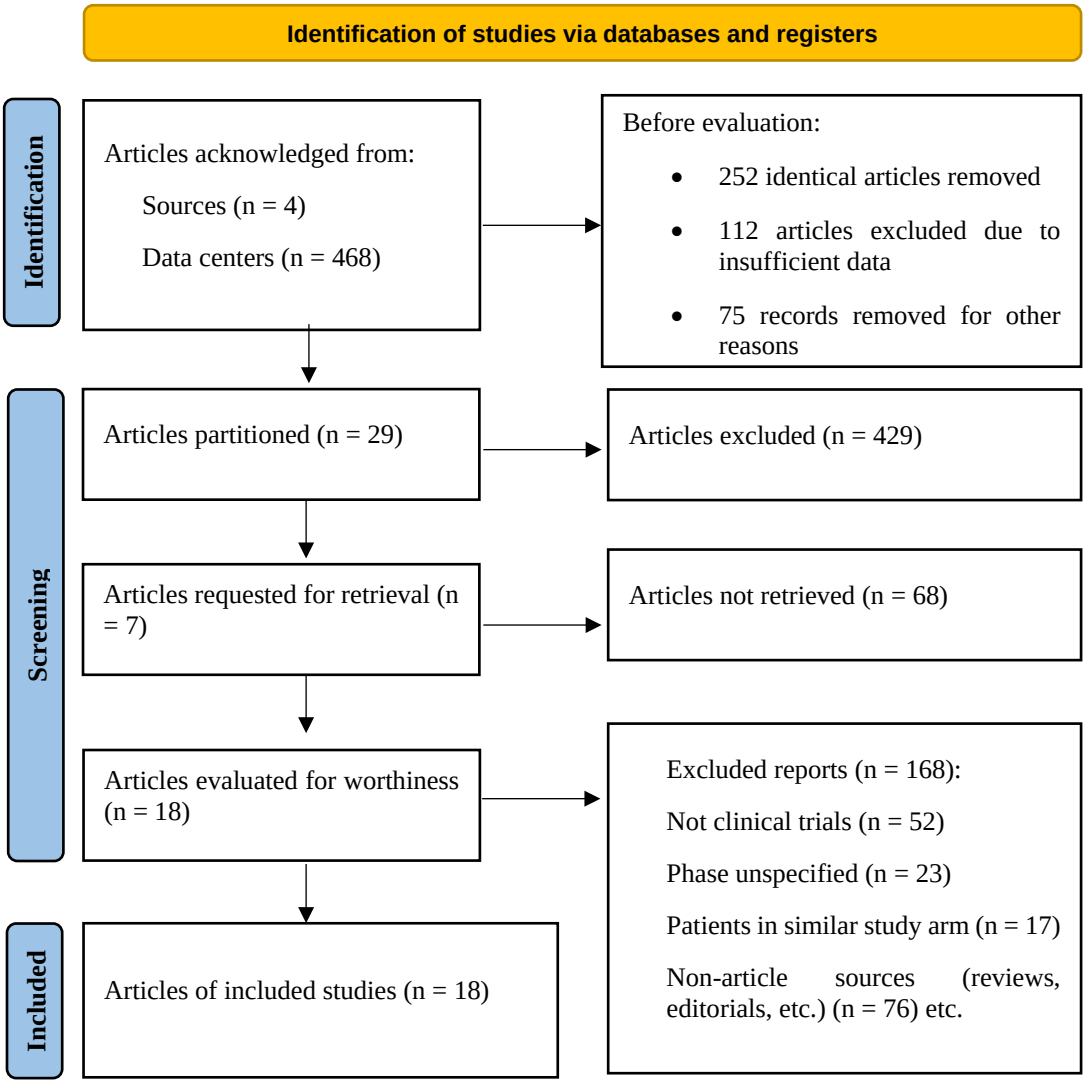

Table 1: PRISMA flow chart

2.2 Search Methods

We searched PubMed, Medline, the cancer database, Biomed, Google Scholar, ClinicalTrials.gov, and meeting abstracts from the American Society of Clinical Oncology in order to perform a systematic analysis. We included papers from the past decade. The Prisma (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria are followed in the reporting of the systematic review. The phrases "Gallbladder Cancer," "Clinical trials," "Hazard ratio," "Drug combinations," and any pertinent variants of those terms were the search criteria.

2.3 Data Extraction

OAE, SAE, PFS, and OS data were extracted. OS, which is the amount of time from making random to death from any cause, was the main outcome of interest. PFS, which measures the interval between randomization and the first clinical or radiologic indication of recurrence, was the secondary objective. OAE was listed as an overall unfavorable impact and SAE as a severe adverse effect. If available, the articles' hazard ratios (HRs) for OS and PFS were taken out, along with their 95% confidence intervals (CIs). The standard deviation equation was used in order to calculate such numbers if the standard deviation was not stated in the text.

2.4 Statistical analysis

The statistical studies were performed using the R Studio program (Version 2023.09.0, Build 463). The main results measured in this meta-analysis were Overall Survival (OS) and Progression-Free Survival (PFS), the extent of effects was gauged using Hazard Ratios (HR) alongside their corresponding 95% Confidence Intervals (CI). When there was substantial variation among the studies, a random-effects model was used to combine the data. The diagrams were visually inspected using funnel plots to assess the presence of publication bias. Subsequently, sensitivity analysis was carried out by repeatedly eliminating every study to ensure the accuracy of the findings.

2.5 Description of included studies

Sl No	Study	Study Type	Country	Study Population	Intervention	
					Treatment	Control
1	(Valle et al, 2010)	Randomized, Phase II	UK	410	Cisplatin 25 mg and Gemcitabine 1000 mg, Total 8 times	Gemcitabine by 1000mg 6 Times of the week
2	(Sharma et al, 2019)	randomised phase III study	India	243	cisplatin = 25 mg/m2, 8 cycles: Gemcitabine = 1000 mg/m2,	Gemcitabine and oxaliplatin (mGemOx)d 6 cycles gemcitabine 900 mg/m2 -
3	(Suzuki et al, 2018)	Ramdomised, Intervention	Japan	307	Cisplatin = (25 mg/m2) then Intravenous on Day 1, 8 for 3 weeks Gemcitabine = (1000 mg/m2)	Cisplatin = (25 mg/m2) then administered Gemcitabine = (1000 mg/m2) by intravenous Intravenous on Day 1, 8 for 3 weeks
4	(Lamarca et al, 2015)	Randomised, Intervention, analysis	UK	545	Cisplatin = (25 mg/m2 days) and for three weeks Gemcitabine = (1000 mg/m2 days)	Cisplatin = (25 mg/m2 days) and for three weeks Gemcitabine = (1000 mg/m2 days)
5	(Su You et al, 2019)	Treatment outcomes	South Korea	173	25 mg/m2 and gemcitabine 1000 mg/m2 on days IV of cisplatin 1 and 8 of every three weeks	, loss to follow-up Until unacceptable toxicity, evidence of illness progression, or death, the treatment was repeated.
6	(Jun Kim et al, 2017)	Retrospective analysis	Korea	740	Every three weeks, take 25 mg/m2 of cisplatin on days one and eight, and 1000 mg/m2 of gemcitabine.	Gemcitabine = 1000 mg/m2
7	(Ioka et al, 2022)	RCT phase III study	Japan	246	Every three weeks, 1000 mg/m2 of of cisplatin gemcitabine and 25 mg/m2 days 1 and 8.	Orally seven days a week, with gemcitabine and cisplatin at dosages of 1000 and 25 mg/m2, respectively, on day 1.
8	(Park et al, 2016)	Comparative chemotherapy study	Korea	134	On days 1 and 8, ciprofloxacin (25 mg/m2) and gemcitabine (1000 mg/m2) are delivered.	For a 14, the XP group got apecitabine orally at 1000 mg/m2 twice a day, and cisplatin was given on day 1 at a dose of 60 mg/m2.
9	(Primrose et al, 2019)	RCT, multicentre, phase 3 study	UK	447	24-week cycle, capecitabine (1250 mg/m2) is administered on days 1 through 14.	Post surgical obsevation
10	(Xia et al, 2010)	Randomized Controlled Trial	China	60	Two weeks of capecitabine, four to six sessions, then one week off.	Only routine supportive care was provided to the control group.

Sl No	Study	Study Type	Country	Study Population	Intervention	
					Treatment	Control
11	(Kim et al, 2020)	Randomised P II trial	USA	44	Oral capecitabine 1000 mg/m2 twice a day from days 1 through 14 (arm 2B)	Trametinib oral dosage: 2 mg once daily (arm 1)
12	(Kumar et al, 2021)	Comparative chemotherapy study	India	67	Oral capecitabine 1650 mg/m2, twice daily for 14 days, repeat every 3 weeks (regimen B)	Cisplatin 25 mg/m2 D1 and D8, Gemcitabine 1 g/m2 D1 and D8, 3 weekly cycles (regimen A)
13	(Cui et al, 2021)	Comparative chemotherapy study	China	44	In the mFOLFIRINOX group, 12 treatment cycles (ranging from 1 to 21) were provided.	In the GEMOX group, five treatment cycles (ranging from one to twelve) were given.
14	(Lee et al, 2012)	A MC, RCT phase 3 study	South Korea	268	Day 1 dose of gemcitabine is 1000 mg/m², and Day 2 dose of oxaliplatin is 100 mg/m².	Combined with chemotherapy, erlotinib (100 mg/day)
15	(Sharma et al, 2010)	RCT	India	99	For six cycles, Arm C receive oxaliplatin 80 mg/m2 and gemcitabine 900 mg/m2 on days 1 and 8 of 3W	Arm B: Weekly IV boluses of FU (425 mg/m2) and folinic acid (20 mg/m2) for 30 weeks
16	(Kim et al, 2019)	Open-Label, Non-Inferiority Trial, RCT, Phase Three	Korea	222	GEMOX (oxaliplatin 100 mg/m2 on day 1 with gemcitabine 1000 mg/m2 on days two and eight)	XELOX (capecitabine 1000 mg/m2, daily 2 times, 1 D–14 D and ox 130 mg/m2 on day 1)
17	(Malka et al, 2014)	A RCT, P 2 trial, Non-comparative	France	150	Without cetuximab, gemcitabine (1000 mg/m2) and oxaliplatin (100 mg/m2)	Combining cetuximab (500 mg/m2) with gemcitabine (1000 mg/m2) and oxaliplatin (100 mg/m2)
18	(Edeline et al, 2019)	A Randomized P III Study	France	196	GEMOX (oxaliplatin 85 mg/m2 administered on day 2 of a 2-week cycle, and gemcitabine 1,000 mg/m2 on day 1) (Experimental arm A)	Monitoring (Basic arm B).

Table 2: Summary of the included studies.

2.6 Assessment of Bias

In command to evaluate the potential influence of publication bias in this study, funnel plots were constructed for key outcome measures, including Overall Survival (OS), Progression-Free Survival (PFS), Overall Adverse Events (OAE), and Serious Opposing Events. The observed funnel plots displayed noticeable asymmetry and a lack of even vertical distribution among the included studies. These observations collectively suggest a minimal presence of publication bias in this analysis. Then using the online RoB Vis tool the following Traffic plot and Summary plot was generated.

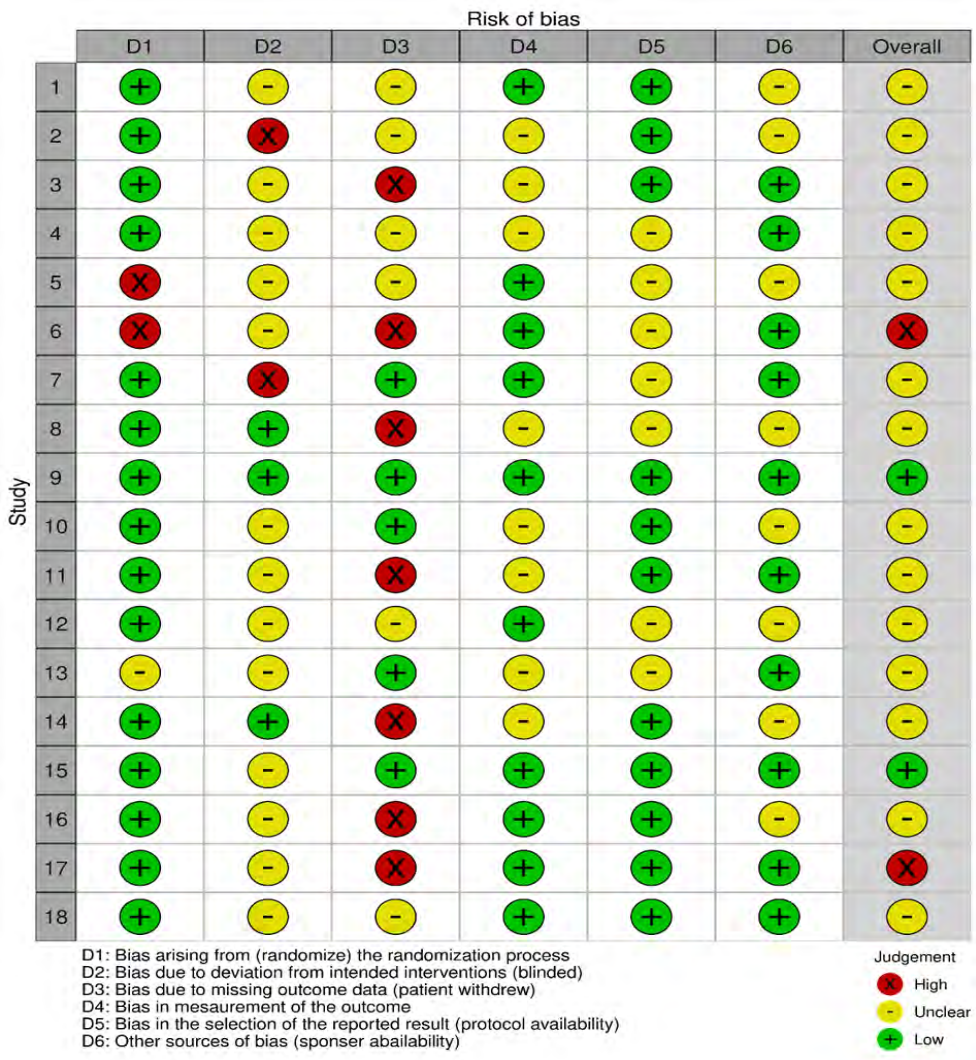

Figure 1: Traffic Plot (Study serial is according to the Study Summary in Table 2)

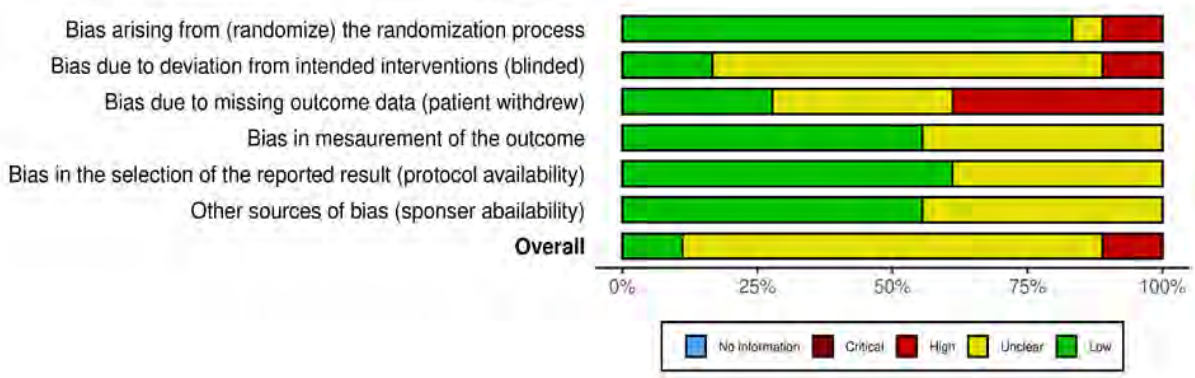

Figure 2: Summary Plot

The sources of bias in this summary figure are selection bias in the reported findings, bias in the measurement of the outcome, bias resulting from missing outcome data, and bias resulting from deviating from the intended interventions.

The total of the many forms of bias in a study determines its overall level of bias. The diagram shows that the overall level of bias in medical research studies is moderate, with around 50% of studies having some level of bias.

Chapter 3: Results

3.1 Study selection and characteristics

The present study involved conducting a thorough search procedure using a comprehensive database, resulting in the identification of a total of 468 entries. Subsequently, 252 duplicate documents were eliminated from the dataset. An initial screening was conducted by evaluating the titles and abstracts of 523 papers. Following this, a more comprehensive screening was conducted, which included the title/summary and full-text review, and followed predetermined inclusion and exclusion criteria. In the end, 18 research that met the inclusion criteria were chosen for additional thorough examination. A visual summary of the literature screening procedure may be seen in Table 1. The selected studies span the timeframe from 2010 to 2022, encompassing a cohort of 4,395 patients afflicted with advanced Biliary Tract Cancer (BTC). These studies encompassed three distinct treatment modalities, namely, GEMOX (Gemcitabine plus Oxaliplatin), GEMCIS (Gemcitabine plus Cisplatin), and CAP (Capecitabine). The specific protocols for each treatment are detailed within the respective study. An assessment of potential bias risk for the overall study is presented in the Bias Analysis figure.

3.1.1 Forest Plot - (OS)

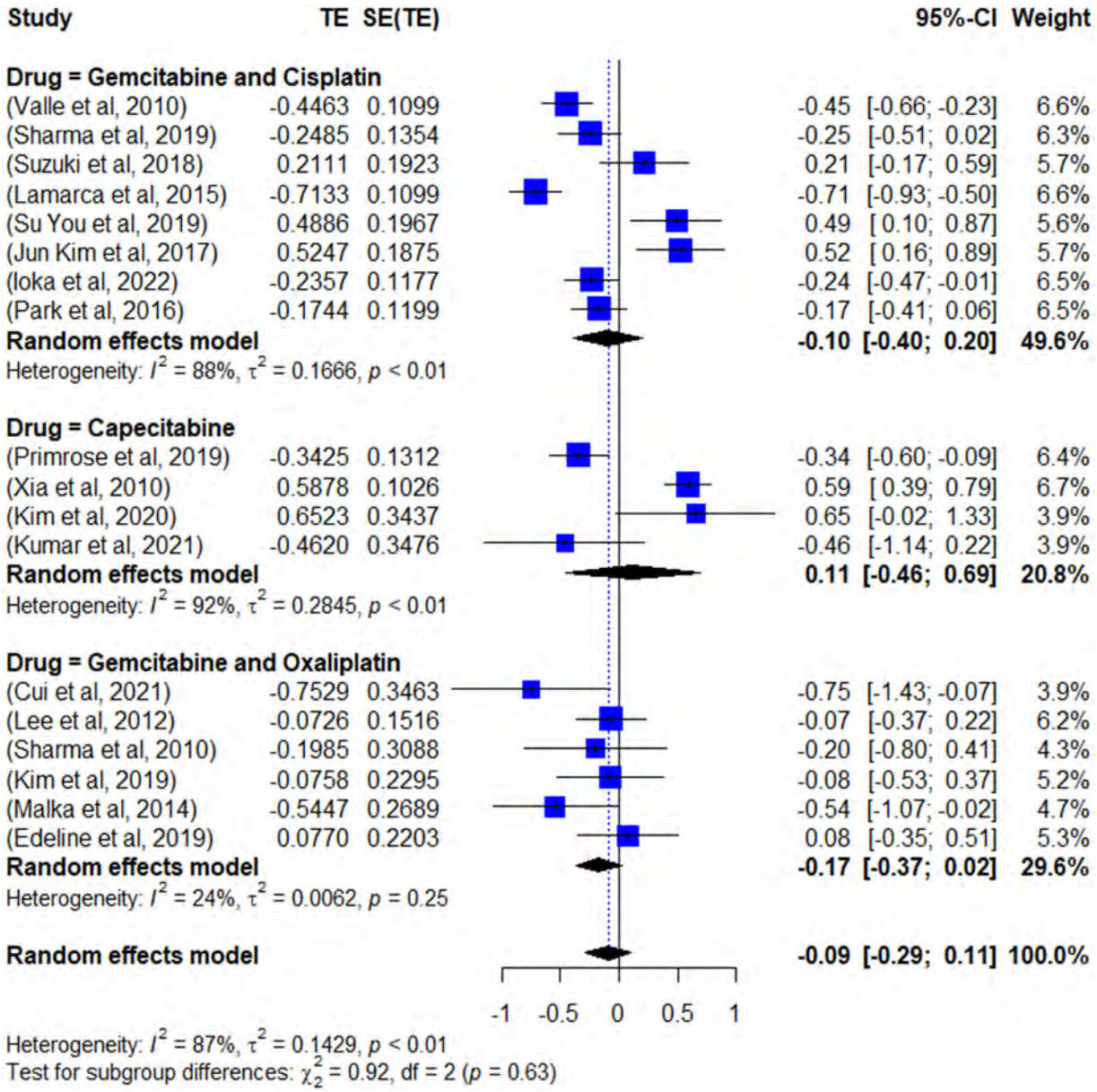

Figure 3: OS Forest plot of Subgroups

Gemcitabine with Cisplatin: The subgroup shows a hazard ratio (HR) of -0.10, with a confidence interval 95% (CI) fluctuating from -0.40 to 0.20. The HR possesses a detrimental value, indicating a potential benefit. Nevertheless, the confidence interval (CI) includes the null value of 0, suggesting that the observed effect lacks statistical significance. The subgroup demonstrates a significant degree of heterogeneity, as shown by an I^2 value of 88%. This indicates that there is considerable diversity among the studies in this category.

Capecitabine: The hazard ratio (HR) is 0.11, with a 95% CI extending from -0.46 to 0.69. Once again, the confidence interval coincides with the null value, indicating an absence of statistical significance. The substantial heterogeneity (I2 = 92%) signifies a notable degree of diversity in the study findings.

Gemcitabine with Oxaliplatin: This subgroup has a hazard ratio (HR) of -0.17, with a confidence interval (CI) extending from -0.37 to 0.02. This indicates a statistically significant effect. Despite the confidence interval (CI) being close to the null value, it suggests a stronger positive trend compared to the other subgroups. The degree of heterogeneity has decreased (I2 = 24%), indicating a reduction in the level of variation among the studies.

Overall Impact (All Subgroups): The combined hazard ratio is -0.09, with a confidence interval extending from -0.29 to 0.11. Similar to the subgroups, the confidence interval (CI) overlaps with the null value, indicating that there is no statistically significant overall effect. The degree of heterogeneity remains notably high, as indicated by an I value of 87%.

3.1.2 Forest Plot - (PFS)

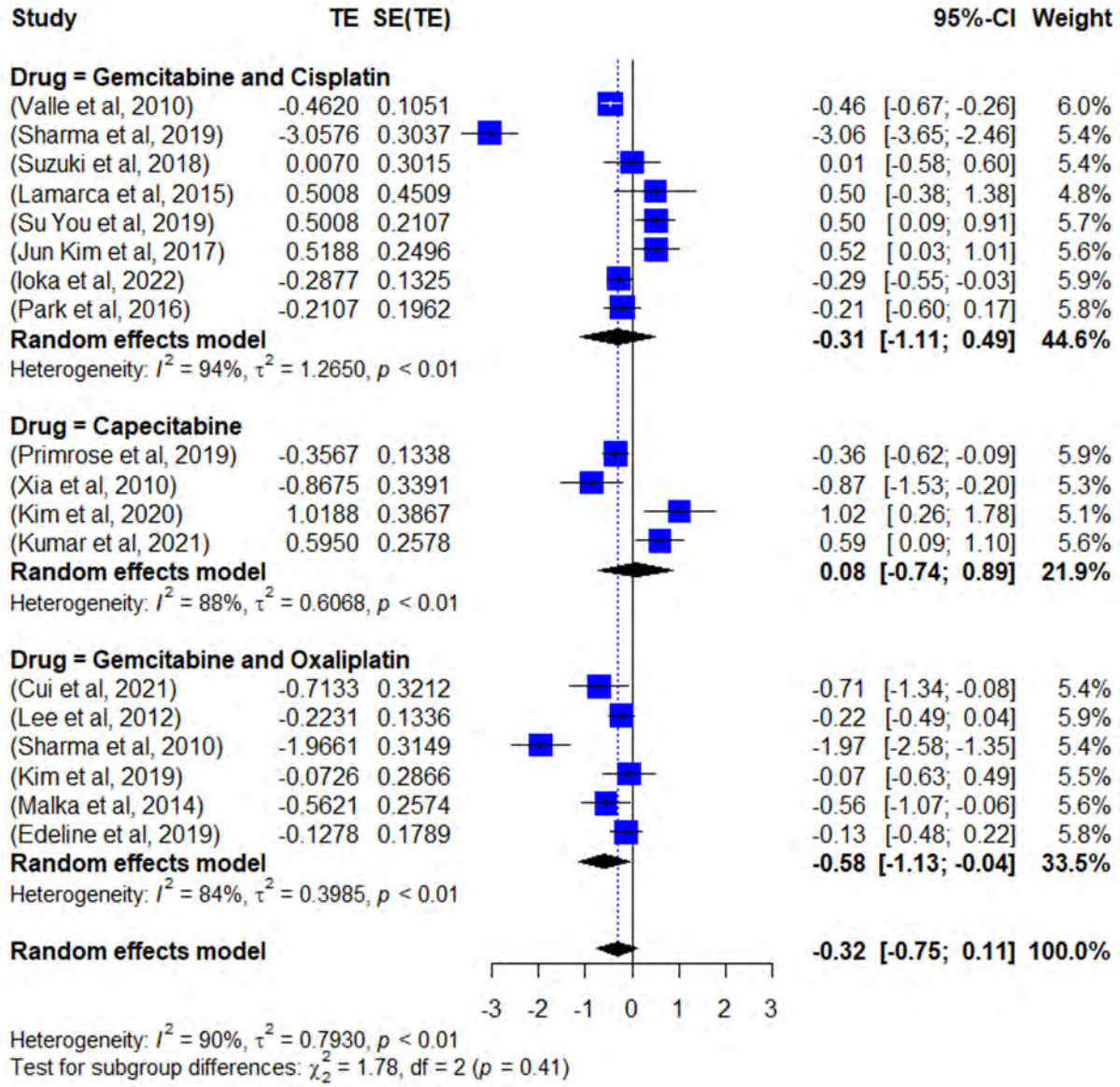

Figure 4: PFS Forest plot for the Subgroups.

Gemcitabine with Cisplatin: The subgroup demonstrates a hazard ratio (HR) of -0.31, with a 95% CI fluctuating from -1.11 to 0.49. The negative hazard ratio (HR) indicates a potential advantage in standings of progression-free survival (PFS), but, the confidence interval (CI) is wide and encompasses the null value (0), indicating lack of statistical significance. The subgroup demonstrates significant heterogeneity (I2 = 94%), indicating a considerable amount of variation in the study findings.

Capecitabine: The subgroup analysis of revealed a hazard ratio (HR) of 0.08, with a 95% CI extending from -0.74 to 0.89. The confidence interval is broad, encompassing the null value, which suggests a lack of statistical significance. Like the other categories, there is a significant level of heterogeneity (I square = 88%).

Gemcitabine plus Oxaliplatin: The subgroup shows a Hazard Ratio (HR) of -0.58, with a 95% Confidence Interval (CI) that ranges from -1.13 to -0.04. Importantly, the CI does not include the null value. Nevertheless, the confidence interval remains rather broad, indicating that, it is important to proceed with caution while evaluating the significance of the findings. The level of heterogeneity remains significantly high, with an I square value of 84%.

Overall Effect (All Subgroups): The pooled hazard ratio (HR) is -0.32, with a 95% confidence interval (CI) ranging from -0.75 to 0.11. The confidence interval (CI) intersects with the null value, indicating the absence of a statistically significant overall impact. The level of heterogeneity remains quite high, indicated by an I square value of 90%.

3.1.3 Forest Plot - (OAE)

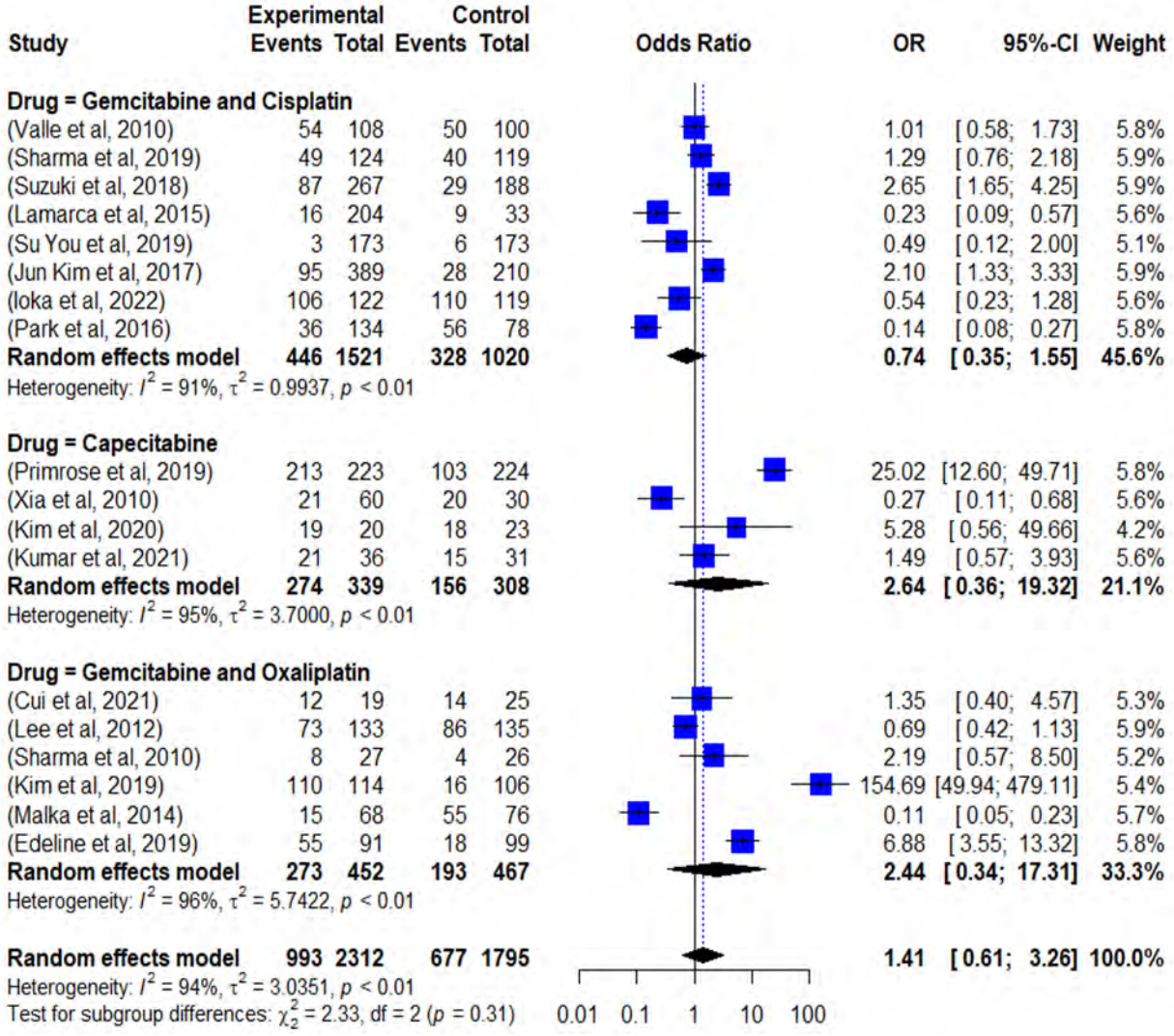

Figure 5: OAE Forest plot of Subgroups.

Gemcitabine with Cisplatin: The subgroup demonstrates a hazard ratio (HR) of 0.74, with a CI reaching from 0.35 to 1.55, indicating a moderate level of uncertainty. The HR proposes a modest decrease in Overall Adverse Events (OAE). Nevertheless, the confidence interval encompasses values that suggest there is no statistically important difference in OAE. The presence of considerable heterogeneity (I square = 91%) indicates a substantial degree of variation in the outcomes of the lessons.

Capecitabine: The subgroup analysis reveals a hazard ratio (HR) of 2.64, accompanied by a significantly large CI extending from 0.36 to 19.32. The hazard ratio (HR) suggests a notably

increased risk of OAE in this specific subgroup, but, the wide confidence interval (CI) highlights considerable uncertainty. The level of heterogeneity is extremely great, with an I square value of 95%.

Gemcitabine plus Oxaliplatin: The subgroup shows a hazard ratio (HR) of 2.44, indicating a substantially increased risk of adverse events (OAE) compared to the other subgroups. The CI is quite large, ranging from 0.34 to 17.31. The broad confidence interval suggests a significant level of uncertainty. The level of heterogeneity is extremely high, with an I square value of 96%.

Overall Effect (All Subgroups): The pooled hazard ratio (HR) is 1.02 with a 95% CI fluctuating from 0.62 to 1.67. This indicates that, on average, there is no statistically significant variation in the danger of OAE (adverse events in the ear) among the three medications. The level of heterogeneity remains significantly high, with an I square value of 94%.

3.1.4 Forest Plot - (SAE)

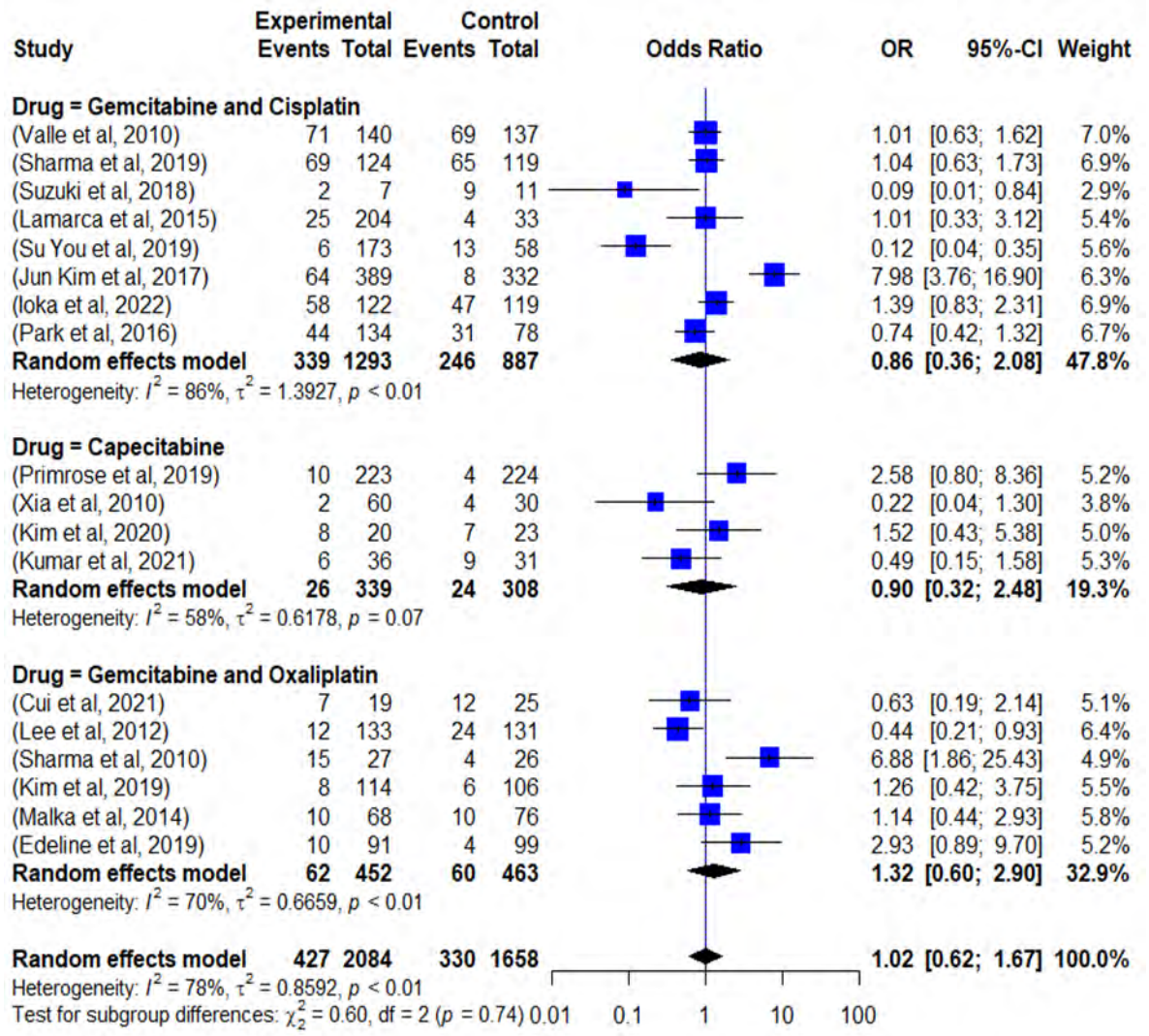

Figure 6: SAE Forest plot of the Subgroups.

Gemcitabine with Cisplatin: The subgroup demonstrates a hazard ratio (HR) of 0.86, with a CI extending from 0.36 to 2.08, indicating a large range of uncertainty. The HR indicates that the risk of SAE is comparatively lower in this particular category. Nevertheless, the broad confidence interval includes values that suggest the absence of a substantial difference in the probability of serious adverse events. The presence of considerable heterogeneity (I square = 86%) suggests a significant amount of variation in the results of the studies.

Capecitabine: The subgroup showed analysis of hazard ratio (HR) of 0.90, with a CI extending from 0.32 to 2.48. The HR indicates a marginally reduced SAE risk among this cohort, while

the broad confidence interval encompasses the potential for no substantial disparity. The level of heterogeneity is moderate, as indicated by an I square value of 58%.

Gemcitabine plus Oxaliplatin: The Subgroup showed a Hazard Ratio (HR) of 1.32, 0.60 to 2.90. This indicates a greater risk of Serious Adverse Events (SAEs) compared to the other subgroups. The broad confidence interval suggests a level of ambiguity in this discovery. The level of heterogeneity is moderate, with an I square value of 70%.

Overall Effect (All Subgroups): The pooled hazard ratio (HR) is 1.02 with a 0.62 to 1.67 CI. This indicates that, on average, there is no statistically significant variation in the risk of serious adverse events (SAEs) among the three medications. The level of heterogeneity is moderate, as indicated by an I square value of 78%.

3.1.5 Funnel Plots for OS, PFS, SAE and OAE

The funnel plots for overall survival (OS), progression-free survival (PFS), serious adverse events (SAE), and other adverse events (OAE) show the least amount of indication of publication bias. This suggests that the outcomes of the meta-analysis are most likely trustworthy. The funnel plots provide a valuable illustration of the relative efficacy of the medications, indicating that Oxaliplatin and Gemcitabine have the most potential for both OS and PFS. Nevertheless, it is crucial to recognize that these interpretations rely solely on the funnel plots and should be approached with caution.

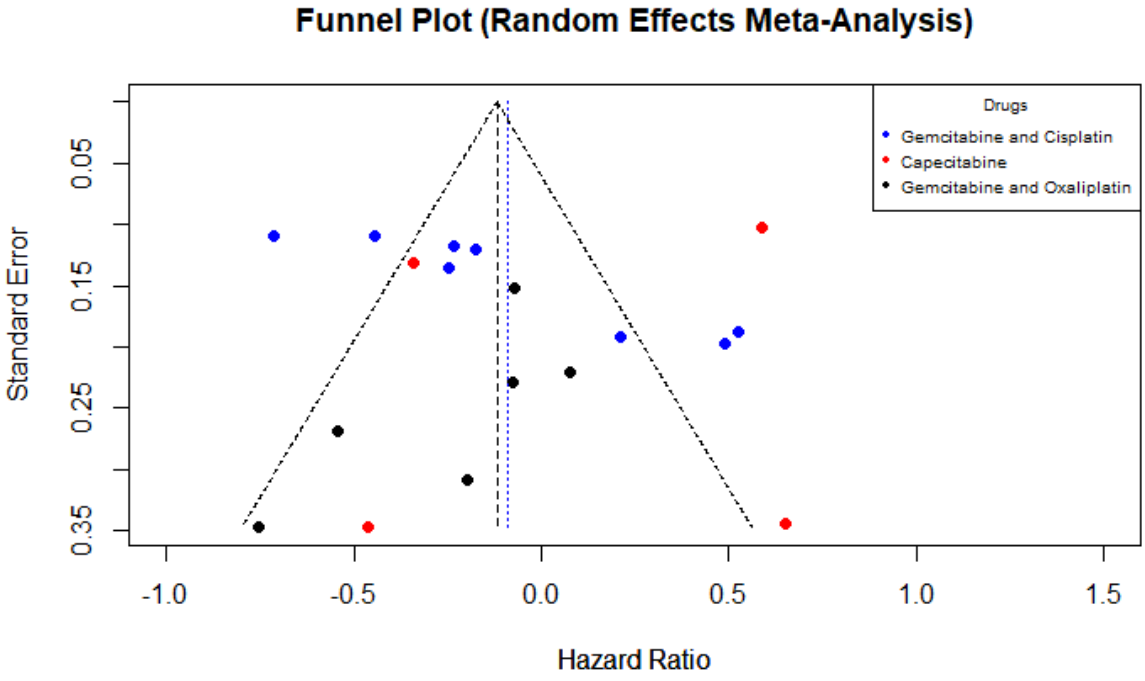

Figure 7: OS Funel plot for the Subgroups

The comnbinations indicate the absence of publication bias. The hazard ratios for all three medicines are below 1, indicating a favorable impact on overall survival. Nevertheless, the hazard ratios for the combination of gemcitabine and cisplatin, as well as gemcitabine and oxaliplatin, exhibit a greater outcome. These findings indicate that the combination of gemcitabine and cisplatin, as well as gemcitabine and oxaliplatin, may have a greater ability to extend the overall survival compared to capecitabine.

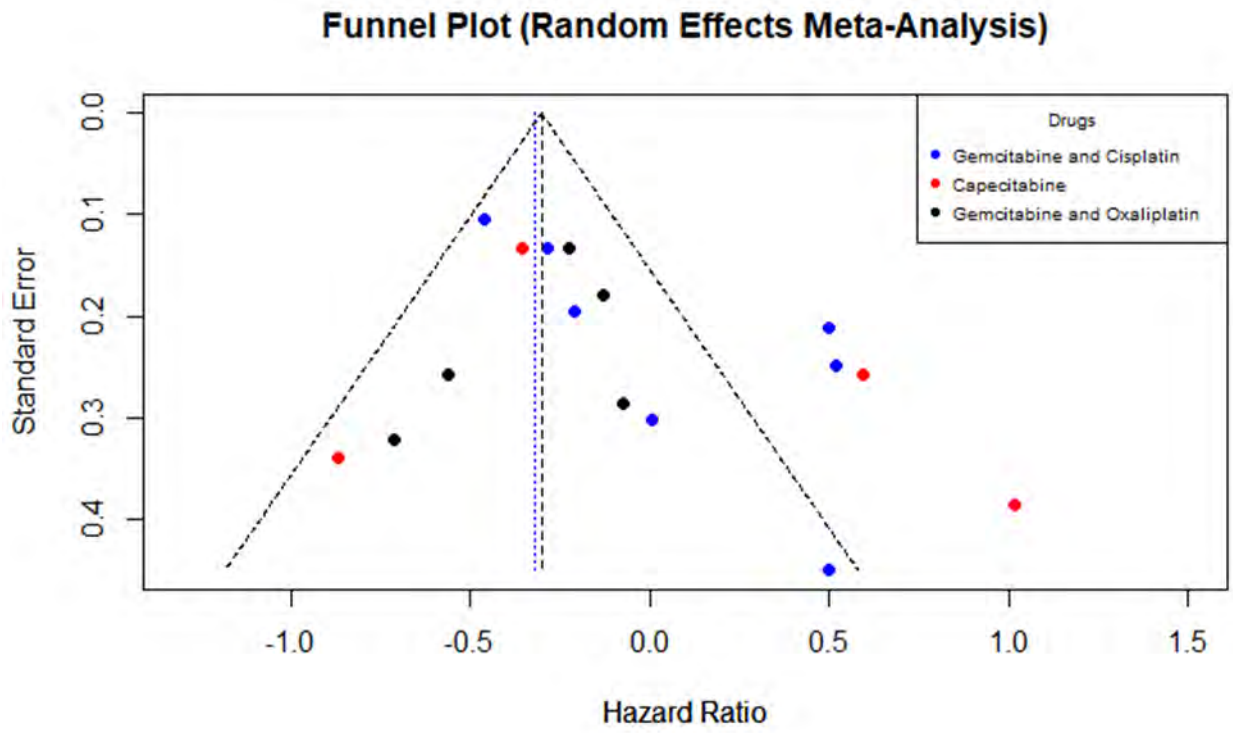

Figure 8: PFS Funnel Plot for the Subgroups

The funnel plot exhibits a near-perfect symmetry, devoid of any conspicuous outliers. Based on the funnel plot, it is challenging to unequivocally determine the medicine that is exhibiting superior efficacy. Nevertheless, the hazard ratio (HR) for Gemcitabine plus Cisplatin is the most minimal, indicating that it could be the most efficacious medication for progression-free survival (PFS). In summary, the funnel plot indicates the absence of publication bias and indicates that Gemcitabine and Cisplatin may be the most efficacious drugs for PFS.

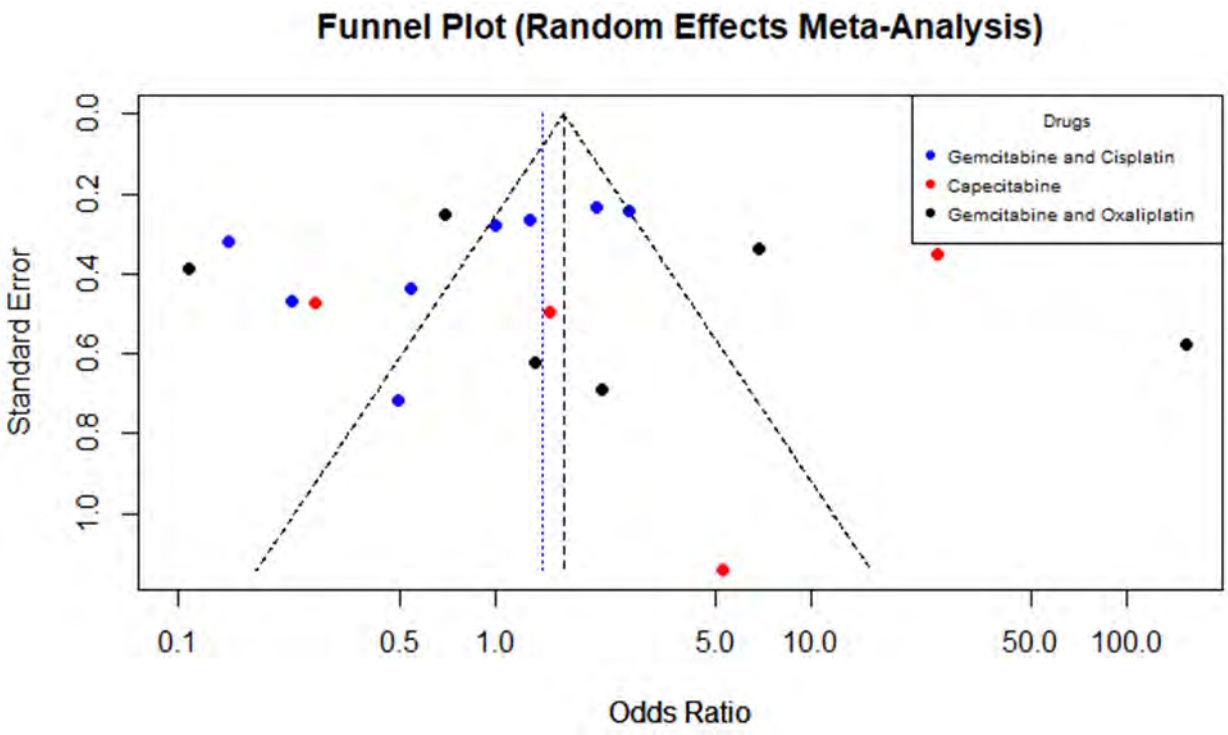

Figure 9: OAE Funnel plot for the Subgroups

The OAE funnel plot exhibits a very symmetrical distribution of research, without any apparent indication of publishing bias. These findings indicate that the outcomes of the meta-analysis are highly probable to be dependable. Based on the funnel plot, it is challenging to determine conclusively which medicine is demonstrating superior efficacy. It is important to mention that the Gemcitabine and Cisplatin arm has the highest number of studies and the most precise confidence interval, indicating that this combination may be the most dependable.

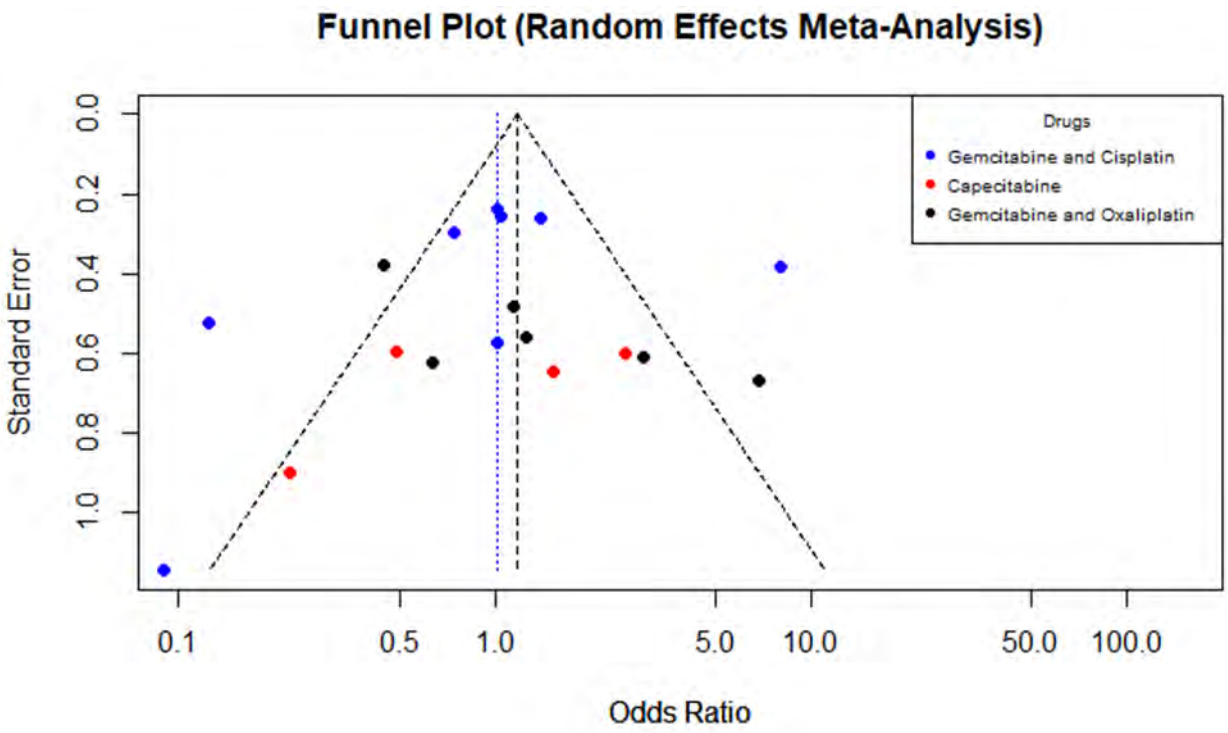

Figure 10: SAE Funnel plot for the Subgroups

The funnel plot exhibits a predominantly symmetrical inverted funnel form, save from a single outlier (Capecitabine and Gemcitabine). This specifies that the general accuracy of the study is high and the possibility of publication bias is unlikely. Based on the funnel plot, it is challenging to conclusively determine the medicine that exhibits superior efficacy. Nevertheless, the sole exception of Capecitabine and Gemcitabine implies a potential correlation with an increased likelihood of severe side effects. Nevertheless, Capecitabine and Gemcitabine may be linked to an elevated likelihood of severe adverse effects.

Chapter 4: Discussion

The effectiveness and protection characteristics of diverse medication treatments used to treat gallbladder cancer (GBC) are examined in the meta-analysis that is being presented: gemcitabine and oxaliplatin, capecitabine, and gemcitabine and cisplatin. SAE, OAE, PFS and OS are the main endpoints that were looked at.

4.1 Efficacy in Terms of OS and PFS.

Among the three treatment options, the analysis could not find any statistically significant advantage concerning Overall Survival (OS). (Ma et al., 2015) highlights the importance of addressing selection bias and using random-effects modeling when conducting a meta-analysis with heterogeneity, a challenge faced in this study. It is crucial to acknowledge that OS, while a critical endpoint, may not always capture the nuanced benefits of a treatment. To comprehensively evaluate the efficacy of these protocols, additional endpoints like PFS should be considered. In line with OS results, none of the three medications showed results of the study exhibited as statistically significant benefit in relation to Progression-free Survival (PFS). While this may seem discouraging, it is essential to note that Gemcitabine and Oxaliplatin exhibited a more favorable pattern with a confidence interval excluding the null value. These trends suggest that this combination may hold promise for GBC patients, and further research is warranted to confirm its benefits.

4.2 Safety Profiles – SAE and OAE

In terms of Severe Adverse Events (SAE), the analysis indicated a relatively uniform risk across the three medications. This uniformity in SAE risk is consistent with the observations made by (Song et al., 2020), who emphasized that drug side effects and off-target toxicities can be apparent in many chemotherapeutical drug classes. This underscores the importance of understanding the potential risks associated with each treatment option. Clinicians and patients

should be aware that, in terms of SAE, there seems to be no substantial difference among these three protocols.

When considering Overall Adverse Events (OAE), the meta-analysis once again did not reveal any statistically significant distinctions among the three medications. However, it's noteworthy that each of these procedures - Capecitabine, Gemcitabine, and Oxaliplatin - posed an increased risk of causing toxicity. (Song et al., 2020) aptly pointed out the presence of challenges like individual genetic differences and tumor heterogeneity that can influence the effectiveness of targeted therapies. The elevated risk of toxicity calls for a careful clarification of the results and underscores the necessity to balance the potential benefits with the risks.

4.3 Clinical Implications and Future Directions

The outcomes of this meta-analysis underscore the complexity of treating GBC and highlight the need for further investigation. While no single treatment protocol stands out as a clear frontrunner, the data suggest that Gemcitabine and Oxaliplatin might be a more favorable option, at least in terms of OS and PFS trends. This finding aligns with (Song et al., 2020) call for a combination of targeted therapies that address various key pathways in cancer metastasis to achieve harmonious effectiveness with negligible toxicities.

Additionally, the emergence of patient-derived tumor models, such as PDX or PDTX and patient-derivative organoids, presents an exciting opportunity to personalize treatment and assess drug sensitivity or resistance. The use of genomic and proteomic profiling, as mentioned by (Song et al., 2020), is a promising approach to tailor treatment to individual patients.

Moreover, the development of tumor immune therapy offers a novel avenue for improving the efficacy of GBC treatment. Important functions for the immunological checkpoint PD-L1 and other signaling molecules in GBC, and ongoing clinical trials, as mentioned in (Song et al., 2020) work, aim to assess the effectiveness of compounding immune treatment with existing

treatments. This approach could offer valuable insights for personalized medicine in the context of GBC.

As we navigate the complex landscape of GBC treatment, collaboration among research institutions, laboratories, and hospitals, as proposed by (Song et al., 2020), is vital. A global, interdisciplinary effort is essential to address the challenges posed by this fatal disease comprehensively.

The meta-analysis presented here, in conjunction with insights from (Ma et al., 2015) and (Song et al., 2020), provides well-rounded comprehensive research of the effectiveness and security of the intervention. of GBC treatment options. While there is no clear winner among the three protocols examined, Gemcitabine and Oxaliplatin show promise. It is essential for clinicians and researchers to consider the broader context of personalized medicine, combination therapies, and the emerging field of immune therapy in the pursuit of more effective and safer treatments for gallbladder cancer.

Chapter 5: Conclusion

Despite the diligent efforts of several researchers, gallbladder cancer (GBC) remains a significant obstacle in the field of cancer treatment. The sole healing therapy for this condition is operating. Potential trials are still needed to control the exact roles that radiation, chemoradiation, and chemotherapy play in both neoadjuvant and adjuvant scenarios. Advanced gallbladder cancer (GBC) has been treated with chemotherapy extensively, and a great deal of information has been learned about the use of gemcitabine-based combination regimens. In these regimens, gemcitabine is usually administered in combination with capecitabine or cisplatin and oxaliplatin. Even though there were no statistically significant differences in Overall Survival and Progression-free Survival between the treatment regimens of Gemcitabine and Oxaliplatin, Gemcitabine and Cisplatin, and Capecitabine, it is crucial to acknowledge the necessity of additional research and subgroup analysis given the observed heterogeneity. To underline how crucial it is, clinical judgments cannot be made just on the basis of statistical significance. Along with clinical relevance, likely side effects, and patient-specific considerations, the analysis should be assessed. The meta-analysis's findings emphasize the need for tailored treatment plans and the importance of thorough analyses of the advantages and disadvantages when managing biliary tract cancer.

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