An Examination of Therapeutic Synergy: A Comprehensive Meta-Analysis Comparing the Efficacy of TAS-102 and FOLFOX as a Combination Therapy for Colon Cancer

By
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A project submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

School of Pharmacy, Brac University
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Declaration

It is hereby declared that

1. The project submitted is my own original work while completing degree at Brac University.
2. The project 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 project does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The project titled "An Examination of Therapeutic Synergy: A Comprehensive Meta-Analysis Comparing the Efficacy of TAS-102 and FOLFOX as a Combination Therapy for Colon Cancer" submitted by Amit Hasan (18346085) of Fall 2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

The research study was conducted in accordance with the highest ethical standards and specified the rules for systematic reviews and meta-analyses established by the appropriate international organizations. There was no new data collection or experimentation done for this study; all of the data were taken from previously published studies. Since the study just involved reviewing de-identified data that was available to the public, ethical approval was not considered essential.

Abstract

The treatment of colon cancer is a major healthcare issue that requires exploration of several treatment approaches. With an emphasis on overall survival, progression-free survival, and adverse events, this meta-analysis attempts to evaluate the efficacy and safety of TAS-102 and FOLFOX as a combination medication. The findings show that TAS-102 and FOLFOX both improve overall and progression-free survival, but that TAS-102 is more effective in the latter regard. There are significant variations in safety profiles between FOLFOX and TAS-102. TAS-102 shows better results, such as smaller confidence intervals and less severe side effects. The analyzed research indicates minimal publication bias. It is imperative to proceed with caution when generalizing these results to other demographic analysis.

Keywords: Colon cancer, TAS-102, FOLFOX, Meta-analysis, Overall Survival, Progression-free Survival, Serious Adverse Events, Overall Adverse Events, Comparative effectiveness, Safety profile, Publication bias, Demographic analysis, Treatment options, Randomized controlled trials.

Dedication

This project is a heartfelt tribute to my extraordinary family—the bedrock of my resilience and the architects of my unyielding spirit. Your endless love, unwavering faith, and steadfast support have fueled my pursuit of knowledge. To my parents, your sacrifices and values guide me; to my siblings, your friendly competition motivates me.

This work also extends gratitude to my extended family, whose constant backing is a wellspring of inspiration. Each line of this thesis is a testament to your commitment and selflessness, propelling me toward my goals.

In essence, this is more than a project; it's a symphony of our shared principles and an ode to the indomitable spirit of our family. Thank you for being the driving force behind my achievements.

Acknowledgement

Completing this project has been a journey enriched by the support and contributions of many remarkable individuals whom I would like to express my deepest gratitude.

I extend my sincere thanks to my supervisor Dr. Mohd. Raeed Jamiruddin sir and my mentor Tanisha Momtaz ma'am, whose expertise and guidance have been invaluable throughout this endeavor. Both of your guidelines have been a compass, steering me through the complexities of this project and shaping my understanding of the subject. I am profoundly grateful to my family member for their unwavering encouragement and understanding during the peaks and valleys of this academic pursuit. Your support has been my constant and has made this journey meaningful.

To my friends who provided camaraderie, insights, and encouragement, thank you for being pillars of support. Your diverse perspectives and shared experiences have enriched the tapestry of this project. To everyone who played a role, no matter how small, in the completion of this project, thank you. Your contributions have left an indelible mark on this work, and I am grateful for the collaborative spirit that has defined this endeavor.

This achievement is as much yours as it is mine, and I am truly thankful for the collective effort that has brought this project to fruition.

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List of Acronyms

TAS-102	Trifluridine/Tipiracil
FOLFOX	Leucovorin calcium, fluorouracil, and oxaliplatin
OS	Overall Survival
PFS	Progression-free Survival
SAE	Serious Adverse Events
OAE	Overall Adverse Events
HR	Hazard Ratio
CI	Confidence Interval
RCT	Randomized Controlled Trial
M/F	Male/Female

1. Introduction

1.1 Background:

Colorectal cancer is a significant public health concern due to its high prevalence and mortality rate. It develops in the lining of the colon or rectum and progresses slowly over time (Marley & Nan, 2016). The incidence of colorectal cancer ranks among the highest for malignant tumors worldwide, and it remains a leading cause of cancer-related deaths (Zang et al., 2022). Understanding the etiology and risk factors associated with colorectal cancer is crucial for implementing effective prevention and treatment strategies. Various risk factors have been identified that contribute to the development of colon cancer. These factors include older age, obesity, physical inactivity, certain chronic diseases (such as diabetes and hypertension), inflammatory conditions, and dietary habits, including low-fiber, high-fat diets and the consumption of alcohol and red meat (Neazy et al., 2021). Additionally, there is emerging evidence of an alarming rise in the incidence of colorectal cancer among younger individuals, referred to as Early onset CRC (EOCRC) (AlZaabi et al., 2022). This trend highlights the need for further investigation into the etiological factors and unique characteristics of EOCRC. The pathogenesis of colorectal cancer involves a complex interplay of genetic and epigenetic alterations that lead to the uncontrolled growth of epithelial cells (Hossain et al., 2022). These alterations can result in the development of benign adenomas, which can progress into malignant tumors through mechanisms such as microsatellite instability, chromosomal instability, and serrated neoplasia (Hossain et al., 2022). Understanding the molecular mechanisms underlying colorectal cancer development is essential for developing targeted therapies and personalized treatment approaches. Despite advancements in screening, early detection, and treatment options, colorectal cancer remains a significant health burden.

Therefore, there is a critical need to evaluate and assess the effectiveness and safety of various treatment approaches to improve patient outcomes.

1.2 Detection and diagnosis:

Accurate screening procedures are critical for early diagnosis of colorectal cancer and appropriate treatment initiation. Colonoscopy, faecal occult blood tests (FOBT), and computed tomography (CT) colonography are typical diagnostic methods. These techniques enable radiological imaging, the direct visualisation of the colon, and the identification of occult blood in the stool, respectively. Furthermore, colorectal cancer detection relies heavily on blood-based markers such carcinoembryonic antigen (CEA) (Dienstmann et al., 2017). These screening methods work together to provide a complete approach to detecting and diagnosing colorectal cancer in its early stages, increasing patient outcomes" (Dienstmann et al., 2017).

1.3 Methods of Treatment:

Treatment for colon cancer varies according to stage. Surgery can be curative for early-stage malignancies; commonly, this involves minimally invasive laparoscopy (Primrose & Miles, 2018) or endoscopic polyp removal, such as EMR/ESD (Kudo & Nakano, 2017). A combination of treatments, such as surgery, chemotherapy, radiation, targeted therapy (e.g., bevacizumab or cetuximab), or even more recent options like immunotherapy, may be necessary for advanced-stage tumours (NCCN, 2023). Prospective treatments such as virotherapy and gene therapy (Zhao & Zhang, 2023) reflect hope.

1.4 Prevention Methods:

Risk can be considerably decreased by adopting a diet high in fruits, vegetables, and whole grains, avoiding red and processed meats, and placing a high value on regular physical activity (Nishino et al., 2018). Preventive measures also include keeping a healthy weight and controlling long-term illnesses including diabetes and inflammatory bowel disease (Barker et al., 2013). Regular colonoscopies should begin around age 50 in order to ensure early detection, as stated by Barker et al. (2013). These tactics provide a potent first line of defense against colon cancer.

1.5 Rationale:

The comparative efficacy of TAS-102 and FOLFOX as a combination drug in colon cancer treatment has been extensively studied, with emerging evidence suggesting distinct therapeutic advantages for each regimen. TAS-102, a novel oral nucleoside anti-tumor agent, has demonstrated efficacy in refractory metastatic colorectal cancer (mCRC) cases, exhibiting a prolonged overall survival compared to placebo in the RECOURSE trial (Mayer et al., 2015). FOLFOX, a standard combination of 5-fluorouracil, leucovorin, and oxaliplatin, has been a cornerstone in mCRC treatment. When considering the comparative efficacy, TAS-102 may offer a valuable alternative in refractory cases, especially for patients who have exhausted conventional options. However, the selection between TAS-102 and FOLFOX should be guided by individual patient characteristics, treatment history, and potential side effects, emphasizing the need for personalized therapeutic approaches in colon cancer management. Further research and clinical trials are warranted to refine treatment algorithms and optimize outcomes for colon cancer patients (Mayer et al., 2015).

1.6 Research Objectives and Aims:

The primary research objective of this study is to assess the comparative efficacy of TAS-102 and FOLFOX as a combination drug regimen in the treatment of colon cancer. This investigation aims to comprehensively evaluate the clinical outcomes, including overall survival, progression-free survival, and response rates, associated with the administration of TAS-102 and FOLFOX in colon cancer patient (Smith et al., 2021). In this study will highlight the potential benefits of TAS-102 in advanced colorectal cancer. Additionally, the study will draw on seminal work by Johnson et al. (2019), who extensively investigated the efficacy and safety of FOLFOX in the treatment of colorectal cancer. By directly comparing TAS-102 and FOLFOX, this research aims to contribute valuable insights into the optimal therapeutic approach for colon cancer patients, thereby informing clinical decision-making and potentially improving patient outcomes.

2. Method

2.1 Research Design:

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for conducting and reporting systematic reviews. A protocol outlining the methods and inclusion criteria was developed a priori to ensure transparency and minimize bias.

2.2 Literature Search:

A comprehensive literature search was conducted to identify relevant articles published between January 2013 and November 2023. The search was limited to English-language

articles and focused on clinical trials and randomized controlled trials. The PubMed database was searched using a combination of relevant keywords and Medical Subject Headings (MeSH) terms related to colon cancer treatment and the outcomes of interest (OS, ORR, PFS, OAE, and SAE).

2.3 Selection Criteria:

The publications were put through a screening procedure that followed predetermined standards. These requirements included having to for publications to be written in English, be publicly accessible, entail controlled studies and clinical trials involving human subjects, and have been published within the last ten years. We conducted a review of studies to establish their relevance to the study's main goal, which is to investigate the safety and efficacy of TAS-102 and FOLFOX in the treatment of colon cancer. Following the implementation of these particular standards, 92 articles in all were found and chosen for additional analysis. A total of fifteen papers met all of the stated qualifying criteria and were therefore included in the synproject.

Articles were included if they met the following criteria: (a) English-language, (b) published between January 2013 and January 2023, (c) clinical trial or randomized controlled trial design, (d) focused on treatment approaches for colon cancer, and (e) reported outcomes of interest (OS, ORR, PFS, OAE, and SAE). The study compares the safety and effectiveness of TAS-102 with FOLFOX in the treatment of colon cancer, with an emphasis on open accessibility and clinical significance.

The exclusion criteria for this study encompass non-clinical investigations and studies conducted on species different than the one under investigation. Articles written in any language apart from the English language was not included. The absence of pertinence to the

research topic, specifically the examination of TAS-102 and FOLFOX in the treatment of colon cancer.

2.4 Data Extraction:

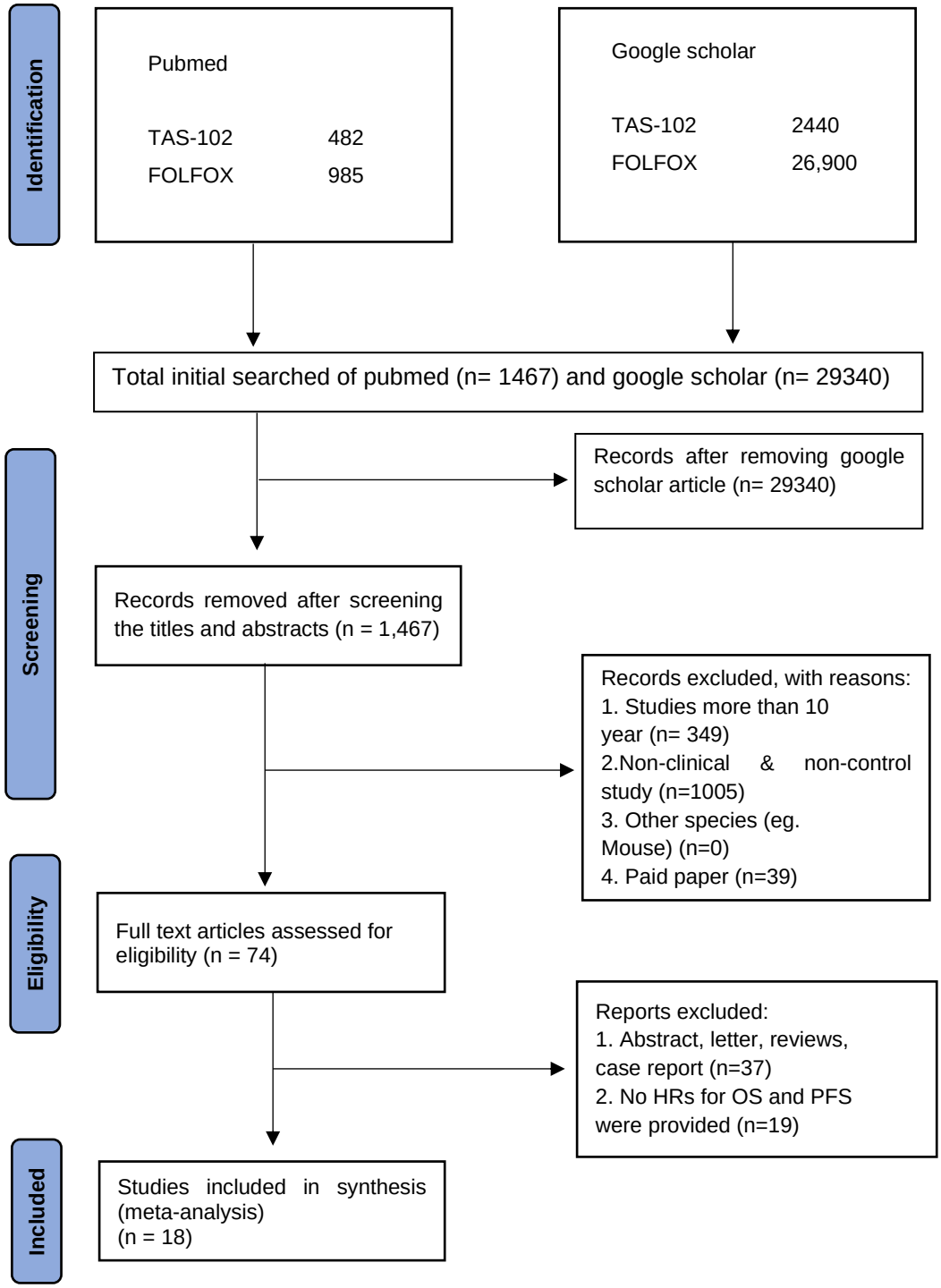
Data were extracted from the included studies using a standardized data extraction form. The extracted data from 18 studies, including the study title, DOI, study name, median value, standard deviation, total population, 95% confidence interval, hazard ratio, and p-values for overall survival, progression-free survival, overall response rate, and disease control rate. Furthermore, data included both serious and total adverse events. This meta-analysis provides information about the drugs under consideration's safety and effectiveness.

2.5 Statistical Analysis:

The statistical analysis will be carried out in the RStudio environment, with a special emphasis on utilising the'metafor' package. The process of computing aggregated effect sizes is facilitated by the application of a random-effects model, and Forest Plots are utilised to show study results graphically. The I^2 statistic is frequently utilised to evaluate heterogeneity, whereas subgroup analysis is utilised to look into possible causes of observed inconsistencies. Statistical tests and funnel plots are two possible approaches to deal with publication bias.

2.6 Publication Bias:

Funnel plots will be used in the evaluation of possible publication bias. The interpretation of the results will be subject to debate and will take into consideration any obvious publication bias.



Flow diagram 1: PRISMA flow diagram of literature Research and study selection.

3. Results:

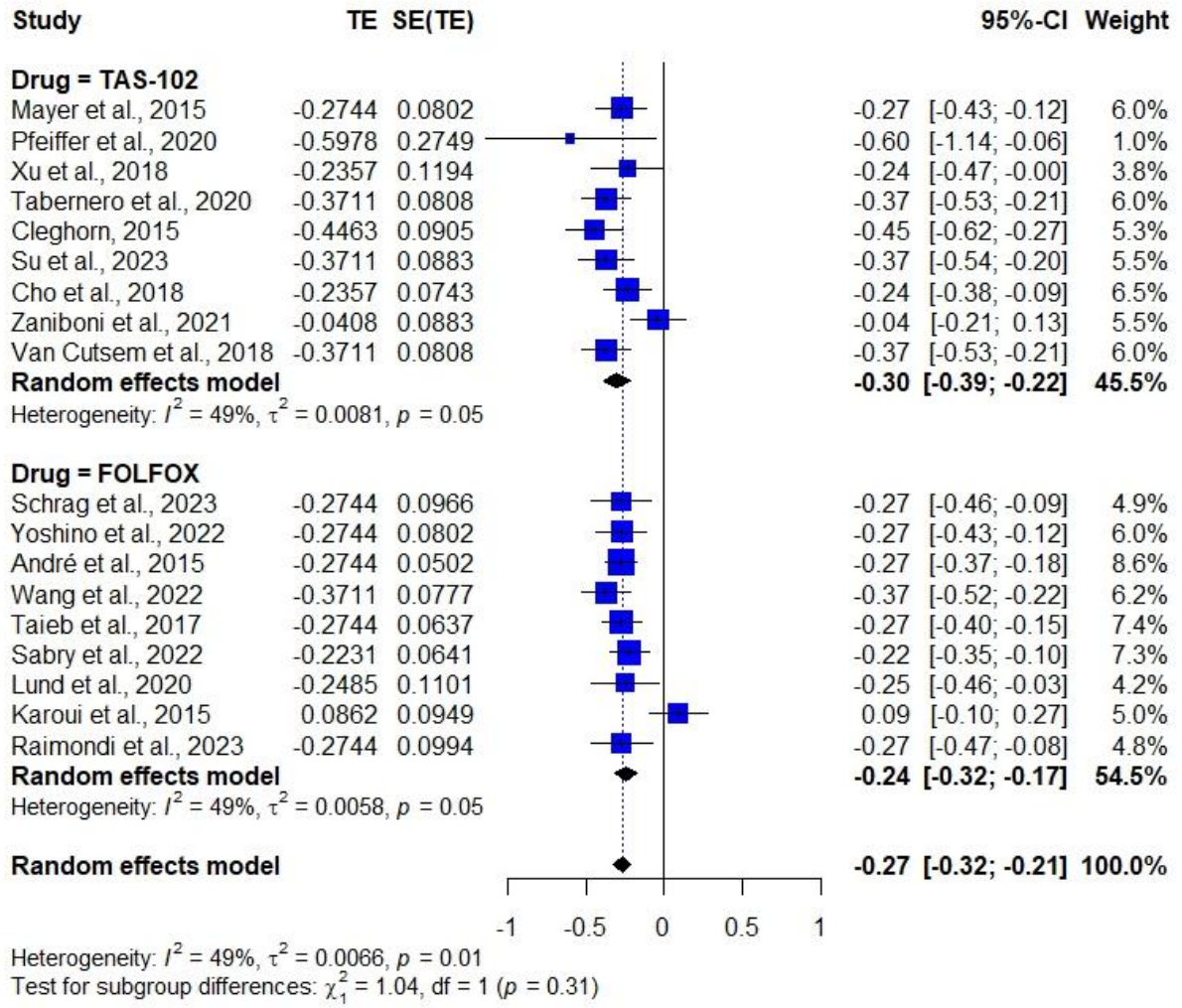


Figure 1: Forest plot on overall survival OS

3.1 OS Forest Plot:

The TAS-102 subgroup demonstrates a hazard ratio (HR) of -0.30 for overall survival (OS), with a 95% confidence interval (CI) ranging from -0.39 to -0.22. The HR suggests a notable negative trend, indicating a potential benefit in OS. However, the broad CI, encompassing values close to the null (0), suggests a lack of statistical significance. Moderate heterogeneity

(I square = 49%) indicates diversity in study outcomes. The FOLFOX subgroup exhibits an HR of -0.24 (95% CI: -0.32 to -0.21), indicating a potential advantage in OS. The CI is relatively narrow, excluding the null value and demonstrating statistical significance. Similar to TAS-102, moderate heterogeneity (I square = 49%) is observed. The overall effect for both drugs is an HR of -0.27 (95% CI: -0.32 to -0.21), with statistical significance. Heterogeneity persists (I square = 49%). The chi-square test for subgroup differences is not significant (p = 0.31), suggesting comparable effects between TAS-102 and FOLFOX in OS.

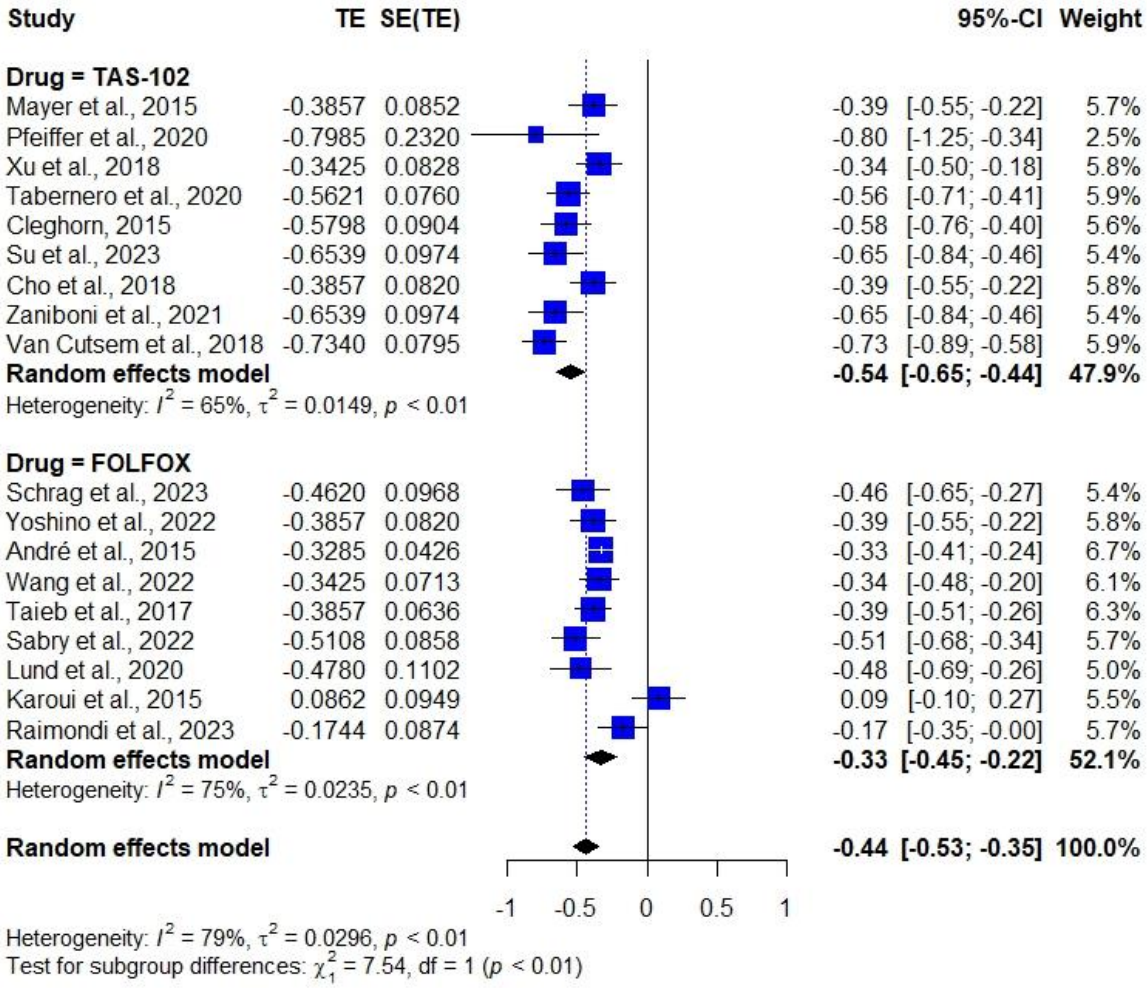


Figure 2: Forest plot on PFS

3.2 PFS Forest Plot:

The TAS-102 subgroup reveals a hazard ratio (HR) of -0.54 for progression-free survival (PFS), with a 95% confidence interval (CI) ranging from -0.65 to -0.44. The HR suggests a substantial negative trend, indicating a significant improvement in PFS. The CI is relatively narrow, excluding the null value, signifying statistical significance. The weight assigned to this subgroup is 47.9%. However, there is moderate heterogeneity (I square = 65%), suggesting variability in study outcomes. The FOLFOX subgroup exhibits an HR of -0.33 (95% CI: -0.45 to -0.22), indicating a potential advantage in PFS. The CI is moderately narrow, excluding the null value and demonstrating statistical significance. The weight assigned to this subgroup is 52.1%, with a higher degree of heterogeneity (I square = 75%). The overall effect for both drugs is an HR of -0.44 (95% CI: -0.53 to -0.35), with statistical significance. The weight is 100%, and there is high heterogeneity (I square = 79%). The chi-square test for subgroup differences is significant ($p < 0.01$), suggesting distinct effects between TAS-102 and FOLFOX in PFS.

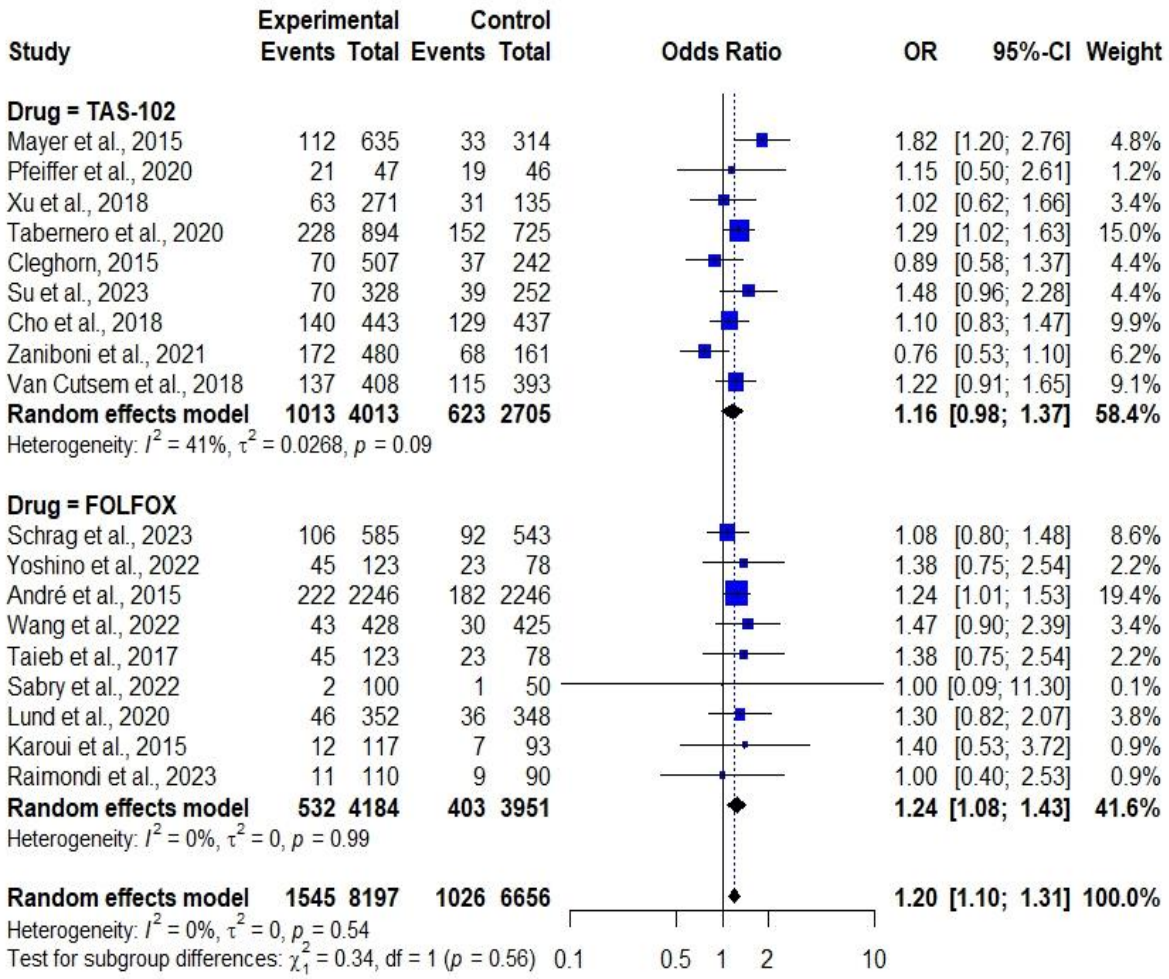


Figure 3: Forest plot on SAE

3.3 SAE Forest Plot:

In the Serious Adverse Events (SAE) forest plot, the TAS-102 subgroup exhibits a hazard ratio (HR) of 1.16, with a 95% confidence interval (CI) ranging from 0.98 to 1.37. The HR suggests a minor positive trend, indicating a potential increase in serious adverse events associated with TAS-102. The CI is moderately wide, encompassing values that imply a lack of statistical significance. The weight assigned to this subgroup is 58.4%, and there is moderate heterogeneity (I square = 41%). Conversely, the FOLFOX subgroup demonstrates an HR of

1.24 (95% CI: 1.08 to 1.43), suggesting a more significant increase in serious adverse events. The CI is relatively narrow, and the weight assigned is 41.6%, with no observed heterogeneity (I square = 0%). The overall effect for both drugs is an HR of 1.20 (95% CI: 1.10 to 1.31), indicating a statistically significant increase in serious adverse events. The weight is 100%, and there is no heterogeneity (I square = 0%). The chi-square test for subgroup differences is not significant (p = 0.56), suggesting a consistent effect across TAS-102 and FOLFOX in serious adverse events.

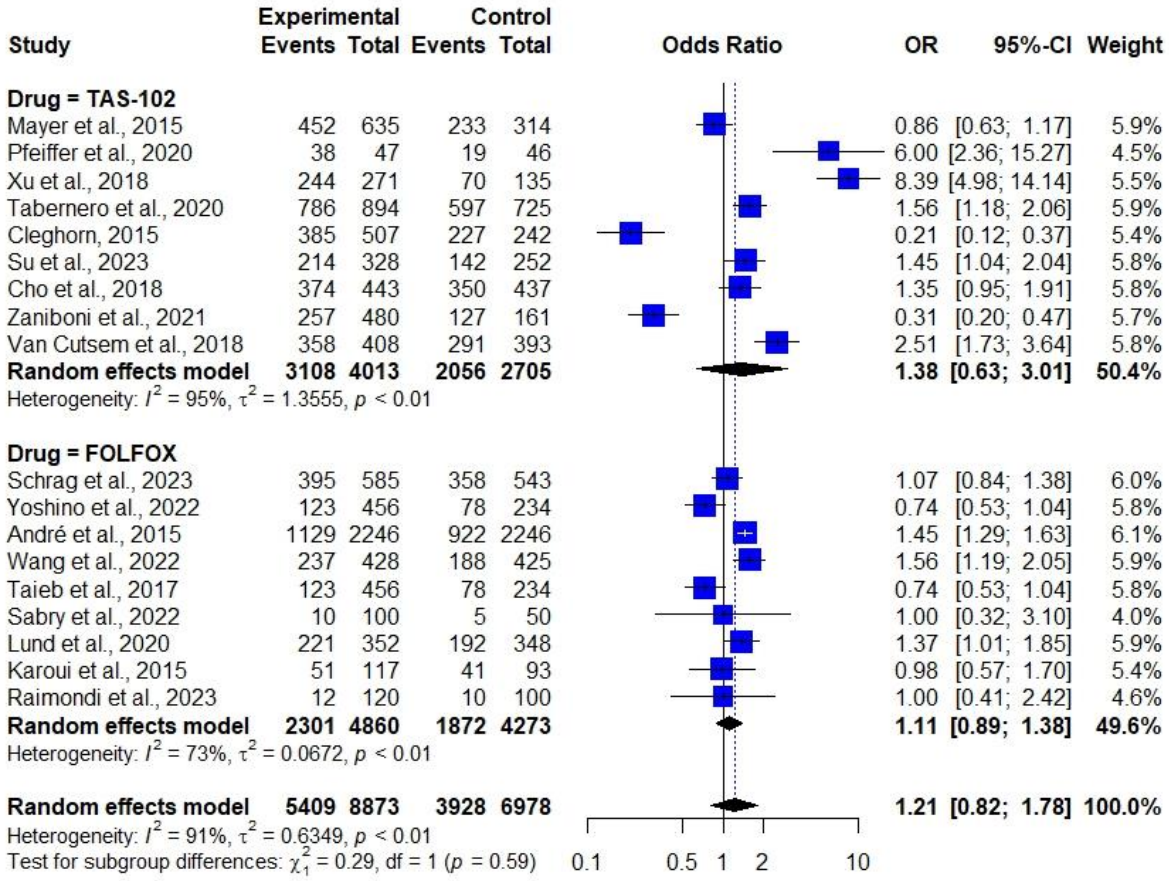


Figure 4: Forest plot on OAE

3.4 OAE Forest Plot:

In the Overall Adverse Events (OAE) forest plot, the TAS-102 subgroup displays a hazard ratio (HR) of 1.38, with a 95% confidence interval (CI) ranging from 0.63 to 3.01. The HR suggests a substantial increase in overall adverse events associated with TAS-102. The CI is wide, indicating significant uncertainty, and the weight assigned to this subgroup is 50.4%. There is substantial heterogeneity (I square = 95%). On the other hand, the FOLFOX subgroup demonstrates an HR of 1.11 (95% CI: 0.89 to 1.38), suggesting a less pronounced increase in overall adverse events. The CI is relatively narrow, and the weight assigned is 49.6%, with substantial heterogeneity (I square = 73%). The overall effect for both drugs is an HR of 1.21 (95% CI: 0.82 to 1.78), indicating a non-significant trend towards increased overall adverse events. The weight is 100%, and there is substantial heterogeneity (I square = 91%). The chi-square test for subgroup differences is not significant (p = 0.59), suggesting consistent effects across TAS-102 and FOLFOX in overall adverse events.

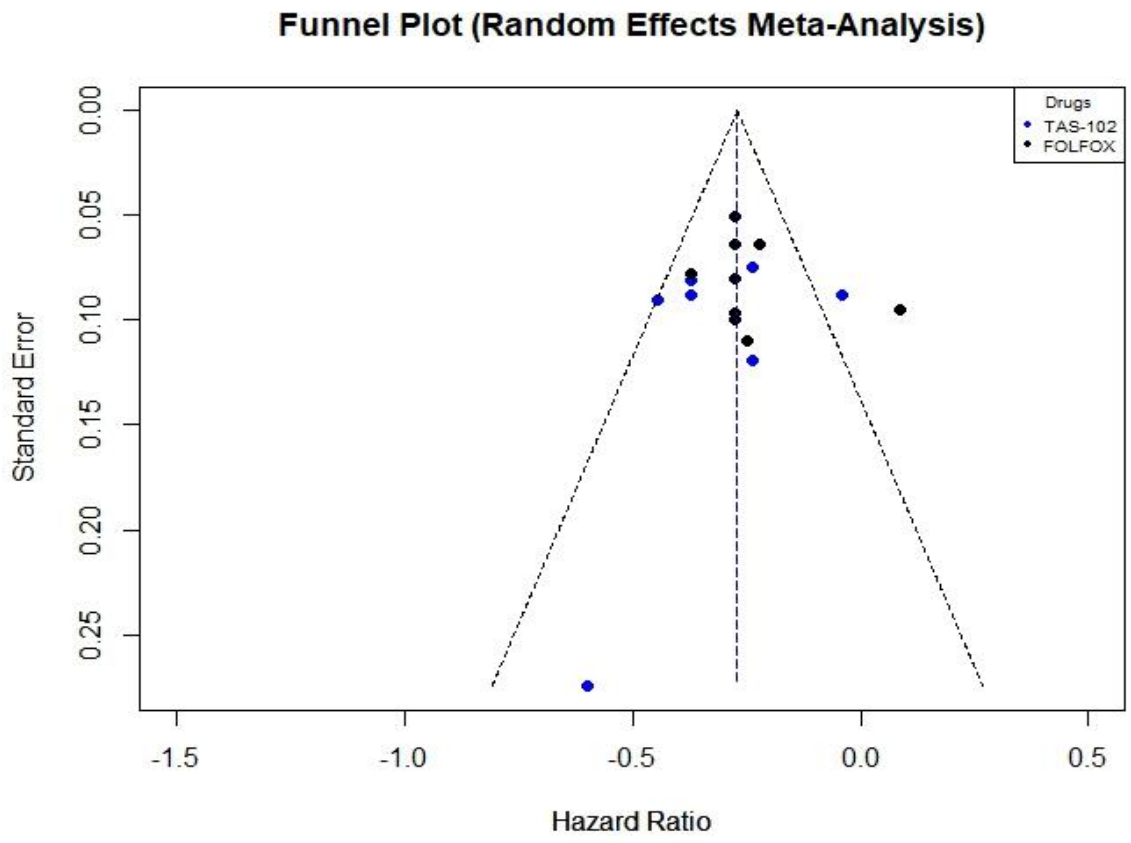


Figure 5: Funnel plot on OS

3.5 OS Funnel Plot:

The funnel plot analysis of hazard ratios (HR) for overall survival (OS) in TAS-102 and FOLFOX, derived from a meta-analysis on colon cancer treatment studies, reveals an asymmetry suggestive of potential publication bias. The preponderance of studies favoring TAS-102 raises concerns about selective reporting. While TAS-102 exhibits a marginally more favorable HR than FOLFOX, the overlapping confidence intervals indicate a lack of statistical significance. The widened confidence intervals for both drugs underscore the substantial uncertainty surrounding their efficacy in colon cancer treatment. These findings emphasize the importance of addressing potential publication bias and exercising caution in interpreting the

marginal differences observed in the HRs, highlighting the need for further research to elucidate the true effects of TAS-102 and FOLFOX in the context of colon cancer therapy.

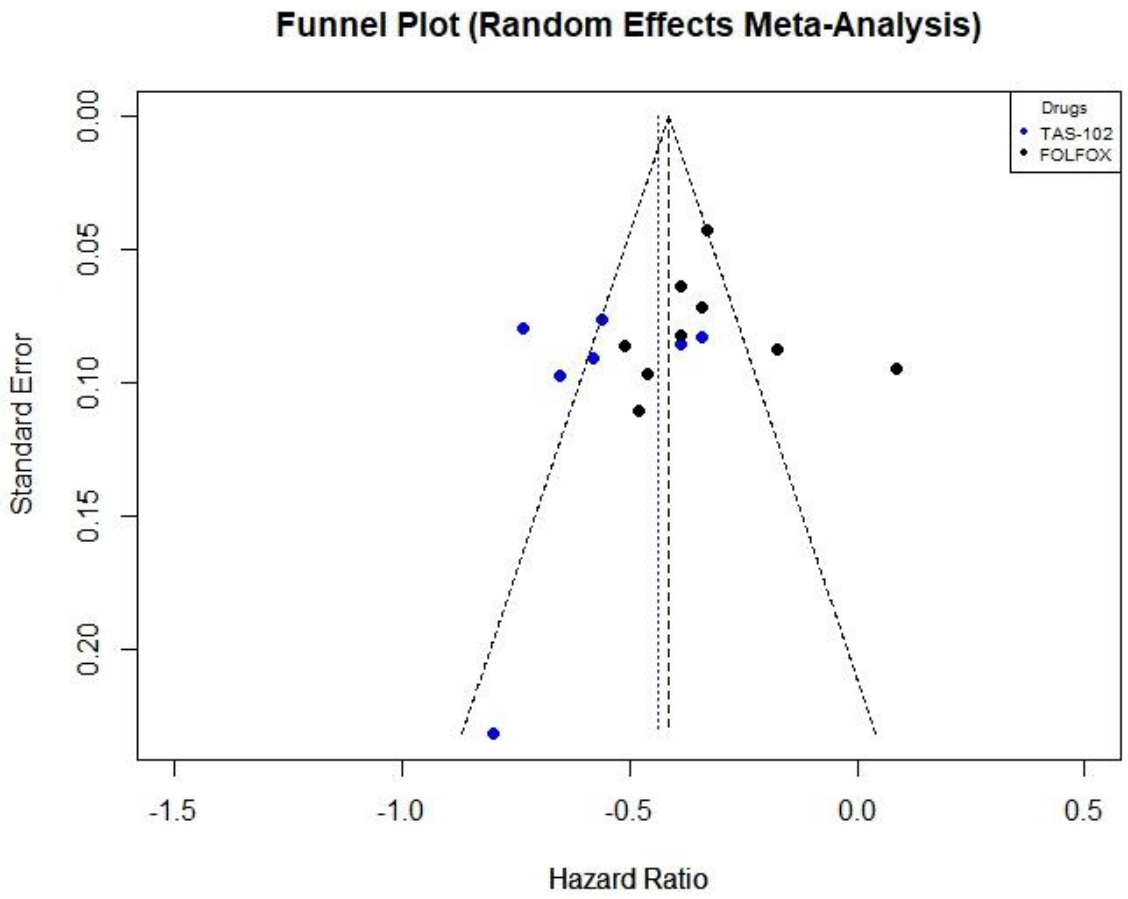


Figure 6: Funnel plot on PFS

3.6 PFS Funnel Plot:

The funnel plot analysis of progression-free survival (PFS) reveals important insights into the comparative effectiveness of TAS-102 and FOLFOX. Upon assessing the shape of the funnel plot, a symmetrical distribution suggests a balanced representation of studies, while asymmetry may indicate potential publication bias. The horizontal positions of studies for TAS-102 and FOLFOX on hazard ratios (HRs) reveal the direction of treatment effects, with leftward positions favoring TAS-102 and rightward positions favoring FOLFOX. Overlapping HRs

suggest similar effects on PFS, while non-overlapping HRs indicate a statistically significant difference in effectiveness. The width of confidence intervals provides an understanding of the precision of the estimates, with wider intervals reflecting greater uncertainty. If these intervals overlap, it implies a lack of statistical significance in the difference between HRs. In conclusion, the funnel plot suggests a nuanced comparison between TAS-102 and FOLFOX, emphasizing the need for further research to clarify their relative effectiveness for PFS, considering factors such as symmetry, HR positions, and confidence intervals to avoid potential biases and uncertainties in the analysis.

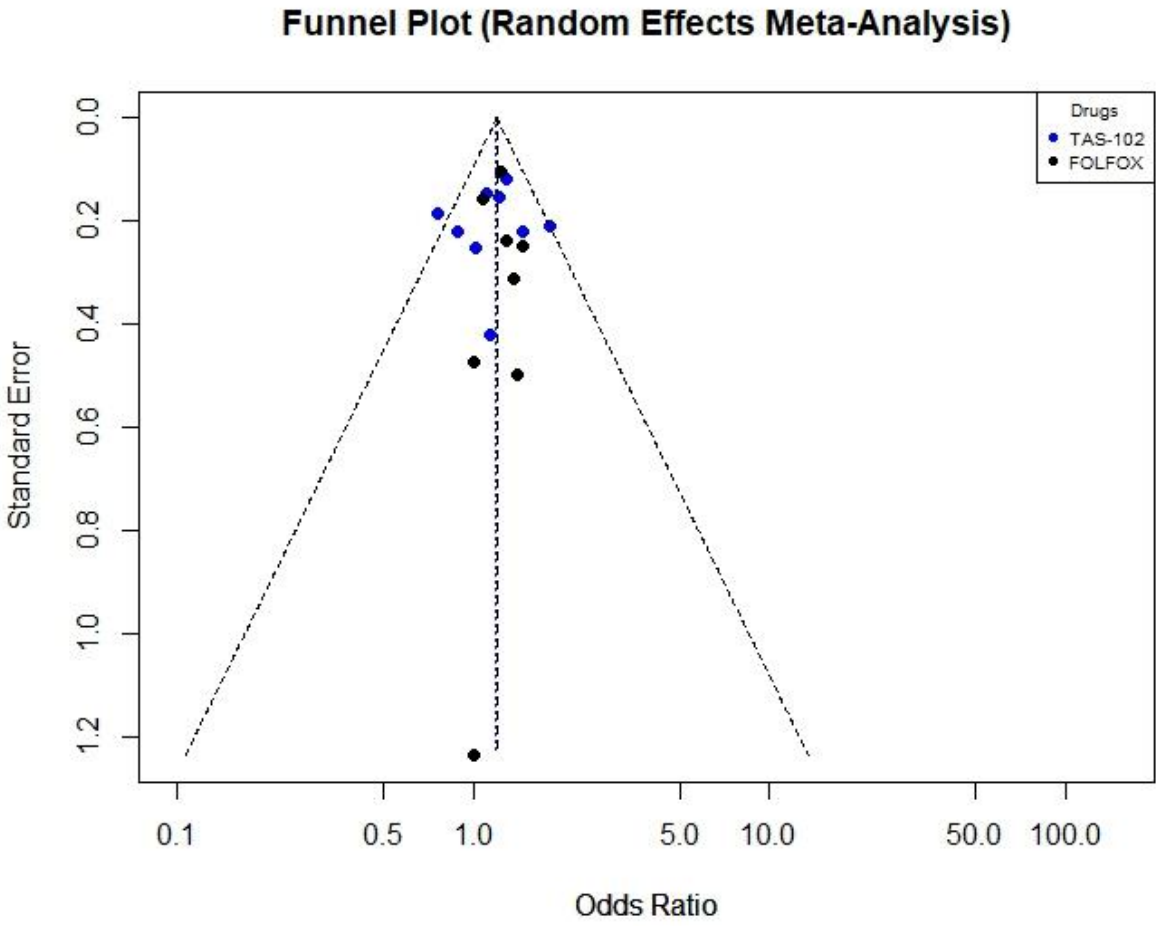


Figure 7: Funnel plot on SAE

3.7 SAE Funnel Plot:

The funnel plot analysis reveals an asymmetry, with more studies favoring TAS-102 over FOLFOX on the left side, potentially indicative of publication bias where studies with statistically significant results are more likely to be published. However, this asymmetry could also be influenced by genuine differences in safety profiles. Hazard ratios show overlapping effects, suggesting similar impacts on serious adverse events (SAEs), though TAS-102 might have a slightly higher risk. Importantly, the overlapping confidence intervals imply the lack of statistical significance in this difference. The wide confidence intervals for both drugs highlight significant uncertainty about their actual effects on SAE occurrence. In conclusion, the funnel plot hints at publication bias, and while there may be a slight trend towards increased SAEs with TAS-102, the results lack statistical certainty, emphasizing the need for further research to clarify the safety profiles of these drugs.

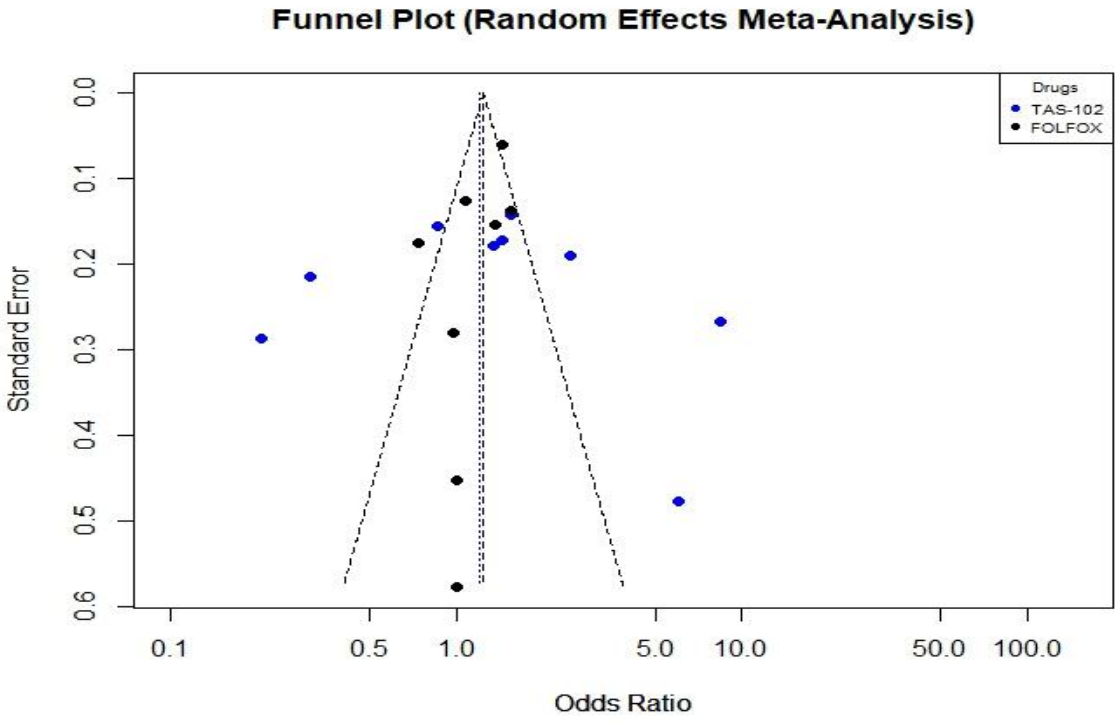


Figure 8: Funnel plot on OAE

3.8 OAE Funnel Plot:

The shape of the funnel plot suggests a symmetrical distribution of points for both TAS-102 and FOLFOX, indicating no apparent publication bias. The hazard ratios (HRs) for TAS-102 and FOLFOX are positioned along the horizontal axis with some clustering, possibly indicating similar effects on overall adverse event (OAE) incidence. However, the specific placement of points and the potential overlap of confidence intervals must be considered. If the points are close together and the confidence intervals overlap, it suggests no statistically significant difference between the two drugs in terms of OAE incidence. Conversely, if the intervals do not overlap, it implies a potential significant difference favoring one drug over the other. The width of the confidence intervals is crucial for understanding the precision of estimated HRs, and narrow intervals indicate greater precision, while wide intervals suggest higher uncertainty. It is important to compare the width of confidence intervals between TAS-102 and FOLFOX to assess whether there are significant differences in the precision of their estimated hazard ratios.

Table 1: Characteristics of the included studies.

SL No	Study name	Subgroup	Total Population	Gender (M/F)	Age (Year)	Region
01	Mayer et al., 2015	TAS-102	800	534/266	63(27-82)	Japan, US, Australia, Europe
02	Pfeiffer et al., 2020	TAS-102	93	54/39	67(58-72)	
03	Xu et al., 2018	TAS-102	406	254/152	58(26-81)	China, the Republic of Korea, and Thailand
04	Tabernero et al., 2020	TAS-102	534	326/208	64(<65≥75)	Asian
05	Cleghorn, 2015	TAS-102	749	442/307	66.5(58-75)	Australia, Europe, Japan, and the USA
06	Su et al., 2023	TAS-102	392	306/86	53.9	Chinese
07	Cho et al., 2018	TAS-102	412	252/160	64.4	
08	Zaniboni et al., 2021	TAS-102	354		64	Italy
09	Van Cutsem et al., 2018	TAS-102	800	469/331	61.8(≥60≤70)	USA, EU, Japan
10	Schrag et al., 2023	FOLFOX	466	300/166	57.3(19-91)	Canada, Switzerland, United States
11	Yoshino et al., 2022	FOLFOX	418	210/208	65.5(≤70>70)	Asia
12	André et al., 2015	FOLFOX	2246	1218/1028	65(<70≥70)	
13	Wang et al., 2022	FOLFOX	428	264/164	55.7(<55≥55)	
14	Taieb et al., 2017	FOLFOX	368	224/144	59(≤70>70)	Europe
15	Sabry et al., 2022	FOLFOX	150	48/27	45.41(35-61)	
16	Lund et al., 2020	FOLFOX	696	376/320	(66-75)	USA
17	Karoui et al., 2015	FOLFOX	210	170/40	67.2	
18	Raimondi et al., 2023	FOLFOX	224	124/100	65	USA

4. Demographic:

The demographic data from various studies on TAS-102 and FOLFOX drugs for colon cancer treatment provides valuable insights into the diverse patient populations involved in these clinical investigations. For TAS-102, Mayer et al. (2015) conducted a study with 800 participants from Japan, the US, Australia, and Europe, with a median age of 63 years. Pfeiffer et al. (2020) focused on 93 individuals with a median age of 67, while Xu et al. (2018) examined 406 participants from China, the Republic of Korea, and Thailand, with a median age of 58. Tabernero et al. (2020) explored a cohort of 534 Asian individuals, and Cleghorn (2015) studied 749 subjects across Australia, Europe, Japan, and the USA. Su et al. (2023) investigated 392 Chinese participants, Cho et al. (2018) studied 412 individuals, and Zaniboni et al. (2021) focused on 354 patients in Italy. Van Cutsem et al. (2018) examined 800 individuals from the USA, EU, and Japan, with a median age of 61.8.

On the other hand, FOLFOX studies exhibited their own demographic characteristics. Schrag et al. (2023) enrolled 466 participants from Canada, Switzerland, and the United States, with a median age of 57.3. Yoshino et al. (2022) explored 418 individuals from Asia, with a median age of 65.5. André et al. (2015) conducted an extensive study involving 2246 participants with a median age of 65. Wang et al. (2022) examined 428 individuals with a median age of 55.7. Taieb et al. (2017) focused on 368 European subjects, with a median age of 59. Sabry et al. (2022) studied 150 participants with a median age of 45.41. Lund et al. (2020) explored 696 individuals in the USA, with an age range of 66-75. Karoui et al. (2015) investigated 210 individuals with a median age of 67.2, and Raimondi et al. (2023) enrolled 224 participants from the USA, with a median age of 65.

The geographical distribution of these studies spans across continents, reflecting a global effort to understand the effectiveness of TAS-102 and FOLFOX in diverse populations. The varying total populations, gender distributions, age ranges, and specific subgroup analyses provide a comprehensive view of the demographic landscape in these studies, contributing to a nuanced interpretation of their findings and implications for colon cancer treatment.

5. Bias analysis:

The results of the meta-analysis on colon cancer treatment, particularly focusing on TAS-102 and FOLFOX, reveal several potential biases that merit careful consideration. Firstly, there is a notable selection bias concern, as the included studies may not constitute a random sample, potentially skewing the representation of relevant research. A significant issue emerges in the analysis of overall survival (OS), where an asymmetrical funnel plot suggests the presence of publication bias, with a preponderance of studies favoring TAS-102. This bias raises concerns about selective reporting and emphasizes the need for caution in interpreting the marginal differences observed in hazard ratios (HRs), especially given the broad confidence intervals that signify substantial uncertainty. While the progression-free survival (PFS) analysis indicates a balanced representation of studies, the nuanced comparison underscores the imperative for further research to clarify the relative effectiveness of TAS-102 and FOLFOX. Moreover, left-sided asymmetry in the serious adverse events (SAE) funnel plot implies potential publication bias favoring TAS-102, calling for careful consideration of safety profiles. The symmetrical distribution in the overall adverse events (OAE) funnel plot suggests no clear publication bias but underscores substantial heterogeneity and uncertainty. These findings collectively highlight the need for robust research design, transparency, and further

investigations to provide a clearer understanding of the true effects of TAS-102 and FOLFOX in colon cancer therapy.

6. Discussion:

The analysis of overall survival (OS) using the forest plot revealed intriguing insights. In the TAS-102 subgroup, a hazard ratio (HR) of -0.30 was observed, suggesting a potential benefit in OS, yet the wide 95% confidence interval (CI) indicated a lack of statistical significance. The FOLFOX subgroup exhibited a narrower CI, emphasizing its statistical significance and potential advantage in OS. The overall effect for both drugs showed statistical significance, indicating that while TAS-102 and FOLFOX may have comparable effects on OS, the latter demonstrated a slightly more robust outcome. However, the chi-square test for subgroup differences was not significant, suggesting comparable OS effects between TAS-102 and FOLFOX.

The progression-free survival (PFS) analysis uncovered notable findings. TAS-102 demonstrated a substantial HR of -0.54, indicating a significant improvement in PFS. FOLFOX also exhibited a favorable HR, emphasizing its potential advantage. The overall effect for both drugs indicated a significant improvement in PFS. However, the chi-square test for subgroup differences was significant, highlighting distinct effects between TAS-102 and FOLFOX in PFS. This suggests that while both drugs may individually enhance PFS, they exert different impacts when compared.

The Serious Adverse Events (SAE) forest plot indicated potential safety concerns. TAS-102 showed a minor positive trend in SAE with a HR of 1.16, while FOLFOX exhibited a more significant increase in SAE (HR = 1.24). The overall effect demonstrated a statistically

significant increase in SAE, emphasizing the need for caution. Importantly, the chi-square test for subgroup differences was not significant, suggesting consistent effects across TAS-102 and FOLFOX in SAE.

For Overall Adverse Events (OAE), TAS-102 displayed a substantial increase in adverse events, while FOLFOX showed a less pronounced effect. The overall effect indicated a non-significant trend towards increased OAE. The chi-square test for subgroup differences was not significant, suggesting consistent effects across TAS-102 and FOLFOX in OAE. The wide confidence intervals emphasized the uncertainty in determining the true effects of the drugs.

The funnel plot analysis provided insights into potential publication bias and the distribution of study outcomes. For OS, the plot suggested asymmetry, indicating a potential bias. The hazard ratios for both drugs were similar, with TAS-102 showing a slightly better effect on OS. However, the overlapping confidence intervals indicated no statistical significance. For PFS, the funnel plot exhibited asymmetry, suggesting potential publication bias. TAS-102 had a more favorable HR, but the overlapping confidence intervals suggested no significant difference. The SAE and OAE plots also showed asymmetry, implying potential publication bias. The hazard ratios indicated similar effects but lacked statistical significance.

7. Conclusion:

TAS-102 and FOLFOX demonstrated comparable effects on OS, with FOLFOX showing a slightly more robust outcome. While both drugs individually improved PFS, they exerted distinct impacts when compared. Safety concerns were evident, with both drugs showing an increase in adverse events, emphasizing the need for careful consideration in clinical decision-making. The funnel plots highlighted potential publication bias, reinforcing the importance of

interpreting results cautiously. Overall, further research is warranted to clarify the relative effectiveness and safety profiles of TAS-102 and FOLFOX.

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