Treatment Response of Immunotherapy Combined with Chemotherapy for Advanced Pancreatic Cancer: A Meta-Analysis

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ABSTRACT

Background: Due to its dismal survival rates and limited treatment choices, pancreatic cancer (PC) continues to be one of the most difficult and aggressive cancers in the world. The potential of immunotherapy (IT) in treating different forms of cancer has led to research on how effective it is in treating advanced pancreatic cancer (APC).
Aims: The purpose of this meta-analysis is to evaluate the efficacy of IT in conjunction with chemotherapy for the management of APC.
Method: Using electronic databases such as PubMed and Google Scholar, a thorough literature search was carried out to find pertinent papers published up until March 20, 2023. Research on the effectiveness and safety of IT in conjunction with chemotherapy for APC were included. The Review manager 5.4.1 was used to conducted an analysis of the included studies.
Results: The odd ratio of the stable disease (SD) and progressive disease (PD) was 1.22 (95% CI: 0.95–1.57), and 0.78 (95% CI: 0.61–1.00), respectively, indicating that there was no significant difference between IT plus chemotherapy and chemotherapy alone. Also, the partial response (PR) of the IT plus chemotherapy did not differ from chemotherapy alone. The odd ratio of partial response was 1.19 (95% CI: 0.80–1.79).
Conclusion: It can be concluded that there was no significant difference in the rates of SD, PD, or PR between the treatment of IT combined with chemotherapy and chemotherapy alone in APC patients. This indicates that the outcomes were similar between the two treatment approaches. However, it is important to note that further analysis and consideration of the full study data are necessary to validate this conclusion.

Keywords: Advanced pancreas cancer, adenocarcinoma, Immunotherapy, Immune checkpoint inhibitors, Chemotherapy

INTRODUCTION

Pancreatic cancer (PC) is a significant contributor to cancer-related deaths globally, ranking as the fourth leading cause. The survival rate for PC is quite low, with less than 9% of patients surviving for five years. Most PC cases are diagnosed at an advanced stage, where the tumor is not surgically removable, leading to a high mortality rate within a year(1). In fact, PC is the seventh leading cause of cancer-related deaths worldwide (2). The symptoms of PC are often vague and appear late in the disease's progression, allowing the tumor to grow undetected. As a result, over 80% of patients are diagnosed with locally

advanced or metastatic PC, which significantly reduces their chances of survival(3, 4).

Surgery is still the only effective treatment for PC, although only a small percentage of people have treatable disease upon diagnosis, and over 80% of patients who have surgery with the intention of curing their condition ultimately relapse and pass away(5, 6). Treatment options for these patients usually involve palliative chemotherapy with drugs such as gemcitabine/nab-paclitaxel or FOLFIRINOX (7, 8). Most patients with advanced PC have limited treatment options and typically undergo chemotherapy. However, PC is a type of cancer that is relatively resistant to chemotherapy. Even for the healthiest patients who can tolerate a combination of three chemotherapy drugs known as FOLFIRINOX, the overall survival is only extended to around 11 months(7). Targeted therapies used in clinical trials for PC patients, without specifically selecting certain patients, have not shown any significant advantages compared to chemotherapy. So far, these targeted therapies have not provided any clinically meaningful benefits(9).

IT has revolutionized the treatment approach for various solid tumors, such as melanoma, non-small cell lung cancer, gastric cancer, genitourinary cancers, head and neck cancer, and selected colorectal cancers (10). However, PC has been more challenging in terms of achieving successful outcomes. Early trials focusing on using immune checkpoint blockade as a single treatment for PC have unfortunately shown disappointing results (11, 12).Furthermore, in PC, the currently available IT options have shown limited effectiveness in terms of extending patient survival (13, 14). Immune checkpoint inhibitors (ICIs) are a type of monoclonal antibody that block specific proteins expressed by tumor cells or immune cells associated with tumors(15). These proteins, like PD-1, PD-L1, and CTLA-4, hinder the activity of T-cells responsible for eliminating cancer cells(16). PD-1 inhibits T-cell activation in peripheral tissues by binding to PD-L1 and PD-L2 ligands(17). Various clinical trials have been conducted to evaluate the efficacy and safety of combining IT with standard chemotherapy options(18). Chemotherapeutic drugs like gemcitabine, FOLFIRINOX, 5-fluorouracil, and Abraxane are commonly used in the treatment of PC. In recent years, IT targeting PD1/PDL1 and CTLA-4 has gained popularity in PC treatment(19). However, the combination of chemotherapy and IT, as well as the use of new targeted drugs or vaccines, have shown conflicting results in terms of survival benefits compared to chemotherapy alone. Therefore, more comprehensive studies are needed to compare the effectiveness of IT combined with chemotherapy versus chemotherapy alone and provide guidance for current clinical practices.

The objective of this meta-analysis is to evaluate and compare the response rates of advanced PC patients receiving IT combined with chemotherapy versus those receiving chemotherapy alone.

METHOD

Search strategy

By searching the major medical databases, PubMed and Google scholar, we identified relevant publications up to March 20, 2023. We used the MeSH form strategy for PubMed as follows: ((Advanced pancreatic cancer (Mesh)) OR (pancreatic neoplasms) AND ((Chemotherapy alone) AND (Immunotherapy)) OR ((Immune checkpoint inhibitors combined chemotherapy)). The publication language was limited in English. To find further relevant publications, a manual search of prior meta-analyses and the references of pertinent studies was conducted. We also utilized the authors' names as search criteria and the PubMed database's "related articles" feature to look for further research.

Inclusion criteria

1. Combination treatment with IT (pembrolizumab, tremelimumab, avelumab, cetuximab, bevacizumab and erlotinib) and chemotherapy (FOLFIRINOX, 5-FU, and Abraxane)
2. Studies with Objective or overall response rate (ORR): Presence of confirmed partial response (PR). such as partial response and stable disease
3. Disease control rate (DCR): the presence of at least confirmed PR or stable disease (SD)
4. Only Published English articles
5. RCT were used.
6. Unresectable advanced, recurrent, or metastatic pancreatic cancer.

Exclusion criteria

1. Animal studies
2. Reviews
3. Case reports

Articles written in a language other than English were excluded.

Data extraction and literature quality assessment

The literature search, screening, and information extraction were independently completed by 1 researcher. When there were doubts or disagreements, the decision or consultation with a second and third party was made after discussion. The content of data extraction included author, year, country, research type, number of cases, partial response (PR), stable disease (SD), and progressive disease (PD). This study independently assessed study quality using the Cochrane Handbook for Systematic Reviews of Interventions version 5.4 risk of bias tool. Sequence generation, allocation concealment, blinding, incomplete data, selective reporting, and other sources of bias were assessed. The term 'high risk' was used to denote studies at high risk of bias in one or more important areas. A study was classified as 'low risk' if it had a low risk of bias in all major domains. Otherwise, it was classified as 'unknown' as shown in Figures 2 and 3. Disagreements between researchers were resolved through discussion with the corresponding author.

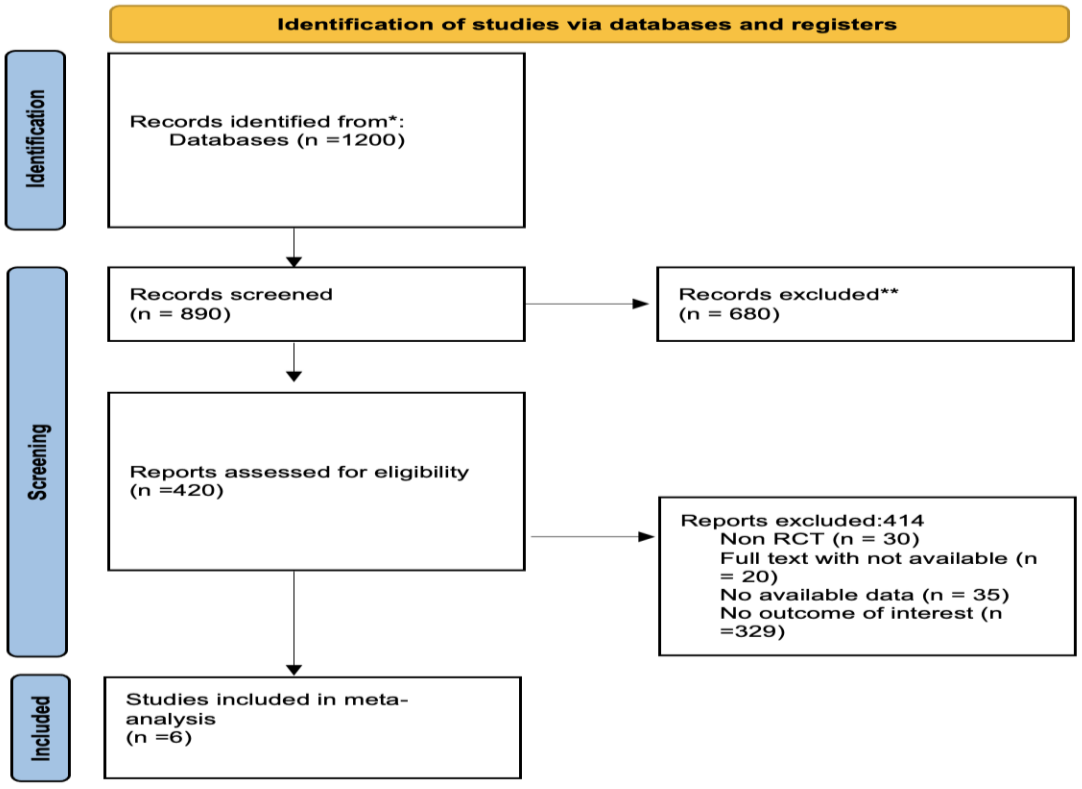

Figure 1.Prisma flow diagram of included studies

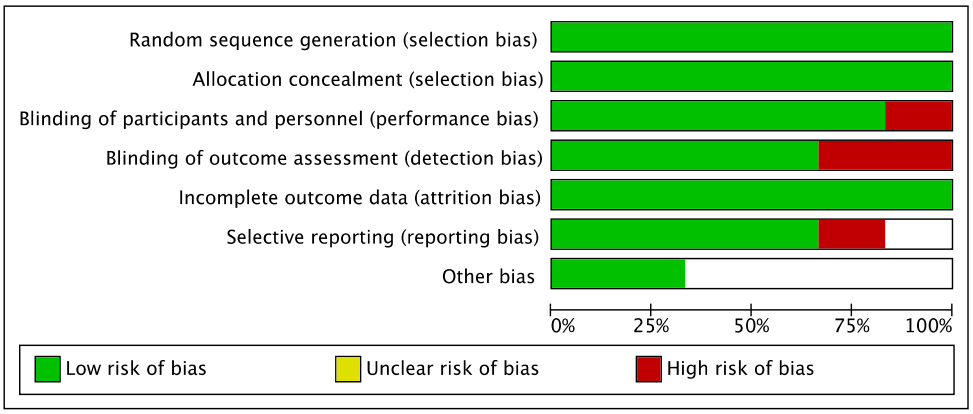

Figure 2.Risk of bias graph

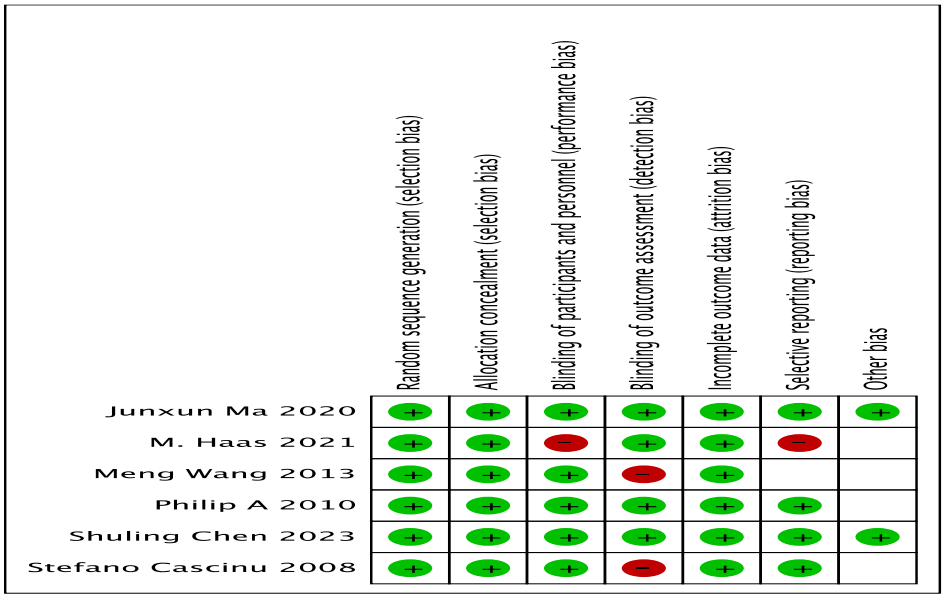

Figure 3.Risk of bias summary

STATISTICAL ANALYSIS

Statistical analysis was carried out using version 5.4 of the Cochrane Collaboration's Software Review Manager (RevMan). We used odds ratios (OR) along with 95% confidence intervals (CI) to combine and analyze dichotomous variables. We calculated both random-effects and fixed-effects models (using OR or RR) using the Mantel-Haenszel statistical method. To evaluate the heterogeneity between studies, we used the consistency statistic (I2). When I2 reached 50%, the pooled results were considered significant and heterogeneous. As a result, we employed a random effects model. Any P-value below 0.05 was deemed statistically significant.

RESULTS

A total of 1200 studies were obtained from the database for this investigation. 890 subjects in total were collected after excluding trials that were duplicates. 420 studies had their eligibility evaluated after titles and abstracts were perused. Six publications were ultimately included in the meta-analysis following the full-text reading, as seen in Figure 1. This meta-analysis contained six RCT trials. The current meta-analysis includes 1,154 patients in total. Table 1 indicates that the patients in three investigations were from China, Italy, Germany, and Canada.

Author	year	Country	Study type	IT plus Chemotherapy	Chemotherapy	PR	SD	PD	Trial number
Stefano Cascinu et al (20)	2008	Italy	RCT	42	42	7/5	15/19	18/17	NCT00536614
Philip A et al(21)	2010	Canada	RCT	372	371	27/23	122/100	118/134	-
Meng Wang et al(22)	2013	China	RCT	28	30	2/2	11/10	15/18	-
M. Haas et al (23)	2021	Germany	RCT	77	38	8/4	32/14	13/12	NCT01728818
Shuling Chen et al (24)	2023	China	RCT	32	64	9/14	20/36	3/14	-
Junxun Ma et al(25)	2020	China	RCT	22	36	4/7	9/14	9/15	-

Table 1.Characteristics of selected studies

Outcome measures

The outcome recorded were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria(26): Partial Response(PR), Stable Disease(SD), and Progressive Disease(PD) .

Definition of terms

1. Objective or overall response rate (ORR), defined as the proportion of patients with a complete response or partial response to treatment.
2. Partial Response (PR): At least a 30% decrease in the sum of the longest diameter of target lesions, taking the baseline sum as the reference. No evidence of new lesion appearance or progression of non-target lesions.
3. Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progression. The sum of the longest diameter of target lesions does not meet the criteria for PR or progressive disease (PD).
4. Progressive Disease (PD): At least a 20% increase in the sum of the longest diameter of target lesions, taking the smallest sum as the reference. The appearance of any new lesion is also considered progression.

PR

Six studies(20, 21, 22, 23, 24, 25), including 1,154 patients, reported the OR of the PR. Since there was no significant heterogeneity (I^2=0.0%, P=0.99>.1), a meta-analysis was conducted using a fixed-effects model. The OR of PR was 1.19 (95% CI: 0.80–1.79), indicating that there was no significant difference for PR between IT combined with chemotherapy and chemotherapy alone, as depicted in figure 4.

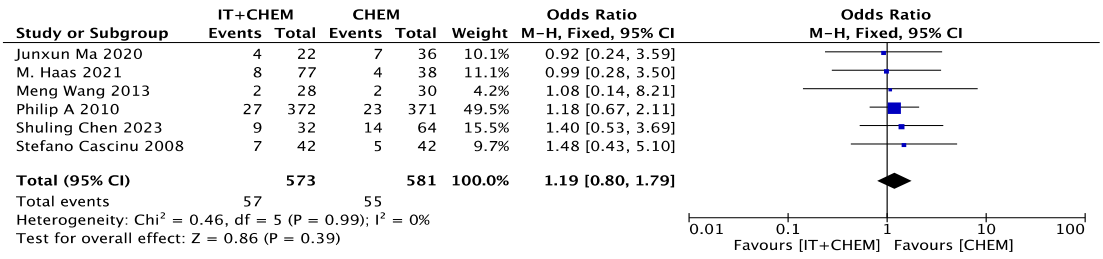

Figure 4.Forest plot of PR

SD

Six studies(20, 21, 22, 23, 24, 25), including 1,154 patients, reported the OR of the SD. Since there was no significant heterogeneity (I^2=0.0%, P=0.84>.1), a meta-analysis was conducted using a fixed-effects model. The OR of SD was 1.22 (95% CI: 0.95–1.57), indicating that there was no significant difference for SD between the two therapeutic arms, as shown in figure 5.

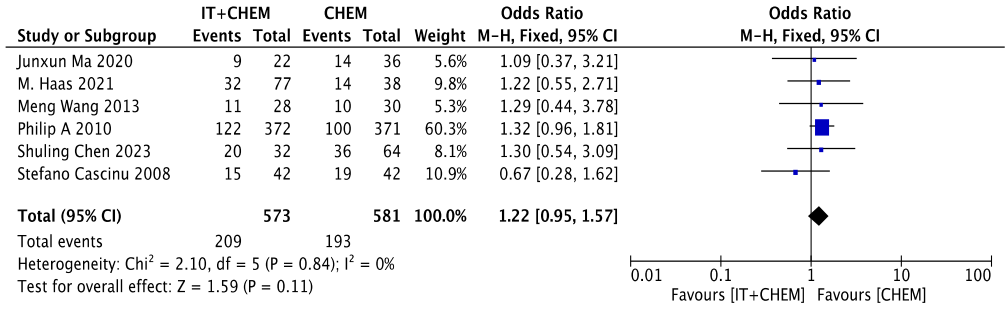

Figure 5.Forest plot SD

PD

Six studies(20, 21, 22, 23, 24, 25), including 1,154 patients, reported the OR of the PD. Since there was no significant heterogeneity (I^2=0.0%, P=0.60>.1), a meta-analysis was conducted using a fixed-effects model. The OR of PD was 0.78 (95% CI: 0.61–1.00), indicating that there was no significant difference for PD between IT plus chemotherapy and chemotherapy alone, as illustrated in figure 6.

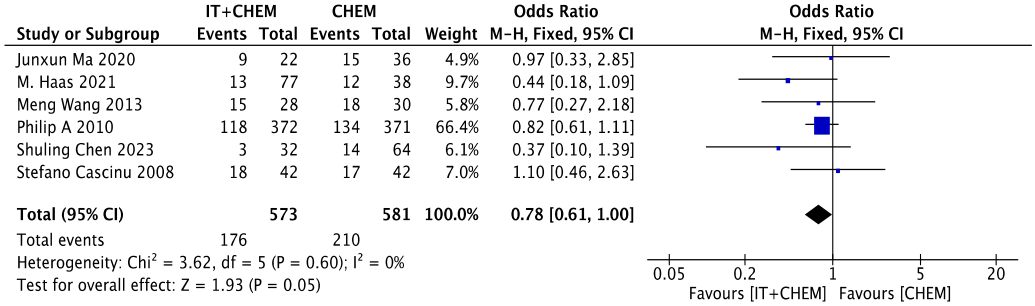

Figure 6.Forest plot PD

Publication bias

Figure 7,8 and 9 shows the funnel plot on PR, SD and PD between IT plus chemotherapy vs. chemotherapy. There is no proof of funnel plot symmetry because every study fell inside the 95% CI range. The results, Heterogeneity: Chi² = 0.46, df = 5 (P = 0.99); I² = 0%, Heterogeneity: Chi² = 2.10, df = 5 (P = 0.84); I² = 0% and Heterogeneity: Chi² = 3.62, df = 5 (P = 0.60); I² = 0%, nevertheless, did not show any proof of publication bias.

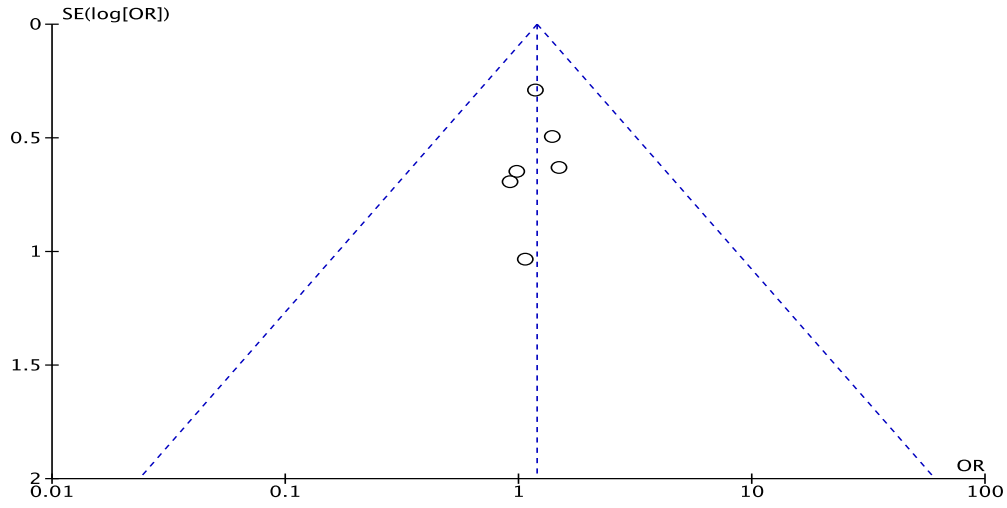

Figure 7.Funnel plot of PR

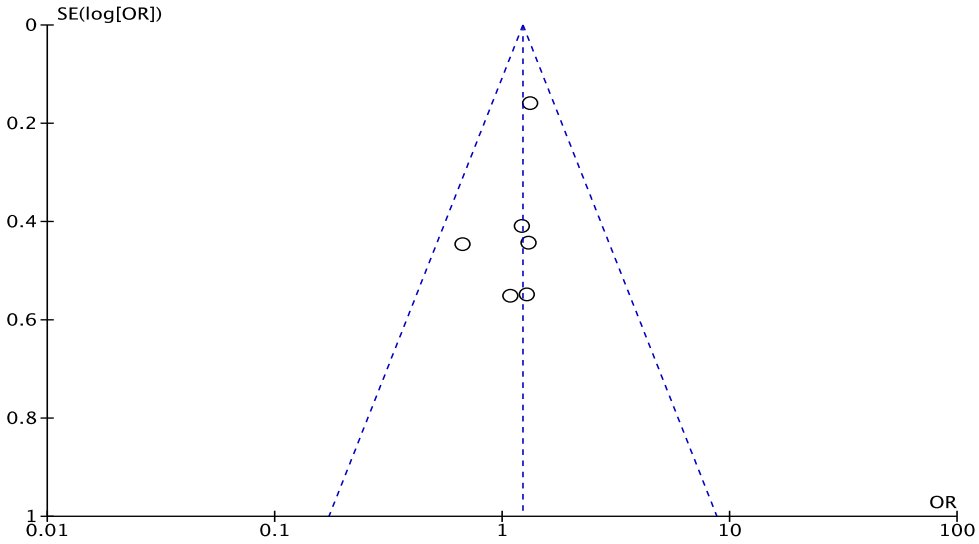

Figure 8.Funnel plot of SD

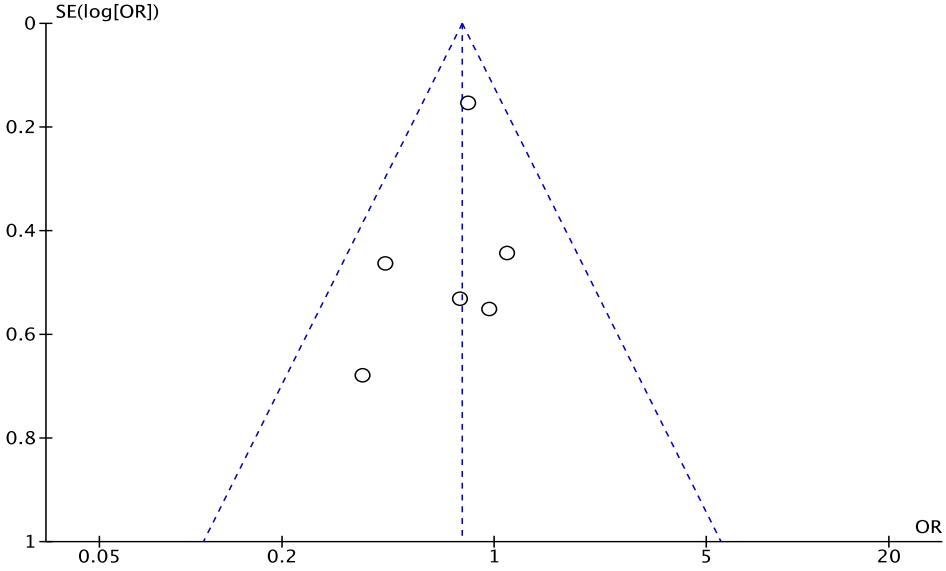

Figure 9.Funnel plot of PD

DISCUSSION

PC has traditionally been treated with chemotherapeutics such as Abraxane, 5-fluorouracil, GEM, and FOLFIRINOX. IT, such as ICIs like CTLA-4 and PD1/PDL1, has been employed increasingly often in PC cases in recent years(19). Regarding the advantages of combined chemotherapy and IT over chemotherapy alone in terms of effectiveness, there is disagreement.

Because PC has biological traits that make it less immunogenic, several research have attempted to increase PC's immunogenicity in order to increase the efficacy of IT (27, 28, 29, 30, 31, 32). Chemotherapy may be beneficial for patients who do not respond well to IT alone because it is thought to induce tumor cell lysis and release tumor antigens (33, 34). The results of this meta-analysis show that, among APC patients treated with IT plus chemotherapy, there was no statistically significant difference in the rates of PD (0.78 95% CI: 0.61-1.00), SD (1.22 (95% CI: 0.95–1.57), or PR (1.19 (95% CI: 0.80–1.79) respectively. This implies that the two treatment modalities produced comparable results. These results add to our existing knowledge of the effectiveness of IT with chemotherapy for APC. A meta-analysis that supported our results found that the combined treatment's disease control rate (1.37%; 95% CI: 1.06–

1.31) was higher than chemotherapy alone, but the ORR risk ratio (ORR) was 1.10 (95% CI: 0.88–1.38), indicating that there was no appreciable difference between the ORR of combination treatment and chemotherapy alone (35). The outcomes of a multicenter phase II study evaluating the combination of cetuximab and gemcitabine in PC patients were presented by Xiong and associates. Dong Song and collogues also noted an ORR of 25% in eight patients who were administered with ICIs combined with chemotherapy(36). The findings indicated that patients had achieved a PR of 12%(37). Even though, based on the trial's statistical design, cetuximab plus gemcitabine should only have been taken into consideration if a response of at least 15% was seen, the researchers came to the conclusion that this treatment combination demonstrated encouraging activity in patients with APC. On the other hand, the PR in our research was 9.9%. Nivolumab/chemotherapy was not shown to be clinically beneficial in first-line treatment for patients with metastatic PC in prior research (38). A promising approach for treating PC is cancer IT. Sadly, IT did not produce satisfactory clinical results in large or late clinical trials, as was to be expected in some early studies (39, 40). ICIs , such as CTLA-4 and anti-PD1/PDL1, have also failed to achieve the desired result thus far (41). The overall shortfall of IT viability in pancreatic disease could likewise somewhat be connected with explicit carcinoma-related fibroblasts, which emit CXCL12 and subsequently prevent Lymphocytes from getting to malignant growth cell districts in the stroma (42). It is significant that IT has shown guarantee in different malignant growth types, prompting expanded interest in investigating its possible in PC. Nonetheless, the consequences of this meta-analysis propose that while IT joined with chemotherapy may not give extra advantages contrasted with chemotherapy alone, further exploration is expected to completely assess its true capacity in this particular disease type.

There are several limitations to acknowledge in this meta-analysis. Firstly, the included studies may exhibit inherent biases or confounding factors that were not fully accounted for. Variations in patient characteristics, disease stage, treatment regimens, and follow-up durations among the studies may introduce heterogeneity and affect the overall outcomes. Secondly, the number of eligible studies included in this meta-analysis was relatively small. A larger sample size would increase statistical power and provide more robust conclusions. Additionally, the potential presence of publication bias is a concern. There is a likelihood that positive results may have been more likely to be published, while studies with negative or null results may have been underrepresented. This bias could introduce an overestimation of the benefits of IT combined with chemotherapy. Future research should focus on long-term follow-up and survival rates to address this limitation.

CONCLUSION

In conclusion, while this meta-analysis suggests that IT combined with chemotherapy may not offer additional benefits compared to chemotherapy alone in APC. Further investigation with larger sample sizes, standardized protocols, and long-term survival data is necessary to validate these findings.

Data availability

Data was retrieved from PubMed and Google scholar.

Authors' contributions

All authors participated in the study's conception and design. Mahmud Abdulkadir Magashi made substantial contributions to the reporting of the work. All authors were actively involved in reviewing relevant literature, drafting the manuscript, and revising the final draft. Material preparation, data collection, and data analysis were carried out by MAM, LD, ZS and IAD. MAM authored the initial draft of the

manuscript, while HC revised and proofread it. All authors provided feedback on earlier versions, and the final manuscript has been reviewed and approved by all.

Declaration by Authors

Ethical Approval: Not Applicable

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Conflict of Interest: The authors declare no conflict of interest.

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