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Systematic Review

Survival benefits and safety of chemotherapy regimens for pancreatic cancer: An umbrella review of meta-analyses of randomized controlled trials

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Abstract

Introduction: Several meta-analyses have reported the survival benefits and safety issues of chemotherapy regimens for pancreatic cancer (PC). The aim was to perform an umbrella review to summarize the existing evidence from meta-analyses of randomized controlled trials (RCTs).

Methods: EMBASE, PubMed, Cochrane database of systematic reviews, and Epistemonikos were searched from inception to October 31st, 2021.Methodological quality was assessed using the A Measurement Tool to Assess Systematic Reviews (AMSTAR-2). The quality of evidence was evaluated using GRADE criteria (Grading of Recommendations, Assessment, Development, and Evaluations).

Results: A total of 2,732 records were identified with 24 articles corresponding to 168 meta-analyses in resected/metastatic PC. Two (8.3%) studies were found to be of high methodological quality. Eighty (47.6%) meta-analyses reported survival benefits of using combination chemotherapy, while 88 (52.4%) meta-analyses reported safety outcomes. 78 (46.42%; 36-efficacy, 42-safety outcomes) of the 168 meta-analyses were statistically significant (P ≤0.05). No meta-analyses were found to be of high-quality evidence. Twelve meta-analyses reporting the survival benefits of gemcitabine combinations were graded as moderate quality of evidence. Combination regimen FOLFIRINOX, gemcitabine nab-paclitaxel (gem/nab), and gemcitabine capecitabine (gem/cap) compared to gemcitabine monotherapy were found to improve overall survival (OS) and progression free survival (PFS) for both resected (OS: HR = 0.78 (0.69-0.89); PFS: HR=0.79 (0.66-0.94)) and advanced PC (OS: HR = 0.76 (0.68-0.85); PFS: HR = 0.68 (0.60 -0.78)). One meta-analysis comparing the gemcitabine combination regimens (with Nab/Paclitaxel or Capecitabine) versus monotherapy among metastatic PC patients was upgraded to high quality after a sensitivity analysis excluding small-sized studies (PFS; HR = 0.78 (95% CI, 0.69-0.88)). The remaining meta-analyses were either low or very low quality of evidence.

Conclusion: Our review showed that the use of combination chemotherapy regimens demonstrated survival benefits over gemcitabine monotherapy, which were supported by moderate to high-quality evidence. Gemcitabine combined with taxanes particularly showed high benefits for overall survival but only a modest benefit for progression free survival for metastatic PC. SWOG-1505 study compared perioperative FOLFIRINOX vs gem/nab in patients with resectable PC but no differences in survival was found. To date, FOLFIRINOX and gem/nab have been compared in the perioperative setting but no phase III trials have performed direct head-to-head comparisons for FOLFIRINOX against gemcitabine-based combination treatments in the metastatic setting. In future, head-to-head clinical trials comparing safety and efficacy for FOLFIRINOX vs gemcitabine-based combinations regimens (specifically gem/nab and gem/cap) in the metastatic setting are required.

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Introduction

Pancreatic cancer (PC) is associated with high morbidity, mortality, and poor prognosis. Although accounting for only 2.6% of the global cancer burden in 2022 with an estimated total of 495,773 new cases, this malignancy was the seventh leading cause of cancer mortality, leading to 466,003 deaths worldwide[1]. At its current trajectory, PC is expected to surpass breast cancer as the third leading cause of cancer death by 2025 despite the relatively small number of cases [2]. While overall cancer survival has increased over the last two decades due to superior therapeutic strategies and earlier detection,–improvements in survival for pancreatic ductal adenocarcinoma has been modest [3,4]. For resected PC, there have been significant improvements in survival with adjuvant chemotherapy regimen FOLFIRINOX [4].

Approximately 80% of PC patients have an unresectable disease. Of these, 50% have metastatic disease and 30% have locally advanced disease [4]. Only about 20% are diagnosed in their early stages when surgical resection is possible. For advanced PC, chemotherapy is the mainstay treatment and for resectable PC, although surgery is the primary treatment modality, survival is prolonged with the use of chemotherapy either in the adjuvant or neoadjuvant setting. In current practice, FOLFIRINOX, gemcitabine-nab paclitaxel (gem/nab), gemcitabine-capecitabine (gem/cap), gemcitabine S-1 are commonly used treatment regimens for PC. Other agents such as irinotecan, and platinum agents like cisplatin and oxaliplatin have also been added to the array of treatments for PC, vastly widening the range of chemotherapy agents available [5].

Several meta-analyses of randomized controlled trials (RCTs) have been published that assessed the safety and the survival benefits of different combination chemotherapy regimens for PC. However, no attempt has been made to summarize the findings from these meta-analyses and assess the quality of evidence. Umbrella reviews make it feasible to summarize the evidence from multiple meta-analyses on the same topic [6,7]. This umbrella review aimed to systematically identify relevant meta-analyses of RCTs, summarize their findings, and assess the quality of evidence to provide an aggregate picture of survival benefits and safety concerns associated with different combination chemotherapy regimens for PC. This study could help determine which chemotherapy regimen is optimal for resectable and metastatic PC in terms of both efficacy and safety.

Methods

This umbrella review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [8]. The protocol of this umbrella review has been registered in OSF Registries (https://osf.io/32dze/).

Search strategy

A systematic literature search was conducted in PubMed, EMBASE, Cochrane database of systematic reviews, and Epistemonikos from inception until October 31st, 2021. Additional articles from reference list of included studies were also searched. Our search strategy included PC type, line of therapy, and different chemotherapy treatments. The search strategy is listed in the supplementary documents (eTable 1).

Eligibility criteria

We included systematically reviewed meta-analysis and network meta-analysis (NMA) of randomized controlled trials (RCTs) that compare survival benefits and/or adverse events of at least two or multiple chemotherapy treatment regimens that are used as first line therapy for both resectable and metastatic PC. No language restrictions were applied. When more than one meta-analysis was available for the same research question, we selected the meta-analysis with the largest data set as previously described elsewhere [7,9,10]. We excluded pooled analyses of a non-systematic selection of observational studies, non-systematic reviews, and indirect/mixed treatment estimates from NMA that did not perform grading. We also excluded meta-analysis that provided insufficient or inadequate data for evidence synthesis.

Title and abstract screenings were done independently by two reviewers (CJ, MS). Full text screening of the potentially eligible articles was also done by the same two reviewers. A third reviewers (AK) was consulted in case of any discrepancies.

Data extraction

Data were extracted at the meta-analysis level. The primary outcome for this review was survival. Types of survival included were overall survival (OS) and progression free survival (PFS) /disease free survival (DFS). Adverse events as defined and graded by Common Terminology Criteria in Adverse Events (CTCAE) were also included as a secondary outcome [11]. Definition for each survival outcome and a list of adverse events included in this review is provided in the supplementary materials (eTable 2).

Methodological quality assessment

The methodological quality of each eligible meta-analysis was assessed using A Measurement Tool to Assess Systematic Reviews (AMSTAR-2) [12], and quality was rated as critically low, low, moderate, or high. Two reviewers (AC, SV) independently performed the data extraction and quality assessments, and a third reviewer (AK) was consulted with any disagreements for resolution.

Data synthesis and sensitivity analyses

For each meta-analysis, we reported the summary estimates, corresponding 95% confidence intervals (CIs), heterogeneity with the I^2 statistic, and publication bias according to the original studies. The quality of evidence in a meta-analysis was assessed by using the grading of recommendations, assessments, and evaluations (GRADE) approach [13]. The GRADE approach comprises of five domains 1) risk of bias in the individual studies, (2) inconsistency, (3) indirectness, (4) imprecision, and (5) publication bias and the

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Table 1: Descriptive characteristics of statistically significant studies included for survival outcomes.

First Author; Publication year	Population	Intervention	Comparator	No of studies	total SS	Cases [SS]	Control [SS]	Model						AMSTAR2	GRADE								
								Outcome	Effect metric	Effect size	LCI	UCI	Random/ fixed		ROB	Inconsi-stency	I2 value	Indir-ectness	Imprecision	Publi-cation Bias [yes, no]	Large effect [yes/ no]	Final GRADE evaluation
H. H. Chen 2018 [35]	Resected PC	Gem/S-1	Gem	2	434	218	216	OS	HR	0.59	0.46	0.74	Fixed	Critically Low	S	S	39%	NS	NS	No	No	Low
P. Parmar 2020 [18]	Resected PC	Combination Treatment Gem/Nab FOLFIRINOX Gem/Cap Gem/Erlotinib S-1	Gem	5	3148	1695	1453	OS	HR	0.72	0.61	0.86	Random	Lowv	NS	S	58%	S	NS	NA	No	Low
Kharat 2021 [22]	Resected PC	Combination Treatment Gem/Cap Gem/Nab FOLFIRINOX	Gem	3	2089	1043	1046	OS	HR	0.78	0.69	0.89	Random	Moderate	S	NS	13.20%	NS	NS	No	No	Moderate
H. H. Chen 2018 [35]	Resected PC	Gem/S-1	Gem	2	434	218	216	DFS	HR	0.63	0.52	0.75	Fixed	Critically Low	S	NS	0%	NS	NS	No	No	Low
A. C. Galvano 2020 [36]	Resected PC [R0 resection]	Combination Treatmvent Gem/Cap Gem/Nab FOLFIRINOX	Gem	3	2089	1043	1046	DFS	HR	0.79	0.66	0.94	Random	High	S	NS	20%	NS	NS	No	No	Moderate
P. Parmar 2020 [18]	Resected PC	Combination Treatment Gem/Nab FOLFIRINOX Gem/Cap Gem/Erlotinib S-1	Gem	5	3148	1695	1453	DFS	HR	0.76	0.63	0.92	Random	Low	NS	VS	76%	NS	NS	NA	No	Low
Kharat 2021 [22]	Resected PC	Combination Treatment Gem/Cap Gem/Nab FOLFIRINOX	Gem	3	2089	1043	1046	DFS	HR	0.77	0.6	0.98	Random	Moderate	S	S	78%	NS	NS	No	No	Low

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R. L. Xie 2006 [34]	Advanced PC	Combination Treatment Cisplatin Erlotinib 5FU Oxaliplatin Exatecan Pemetrexed Irinotecan Capecitabine Marimastat Tegafur/uracil Tipifarnib	Gem	22	5886	2932	2954	6-month OS	RR	0.92	0.87	0.97	Fixed	Critically low	NA	NA	NA	VS	S	No	No	Very Low
R. L. Xie 2006 [34]v	Advanced PC	Gem Combination Cisplatin Erlotinib 5FU Oxaliplatin Exatecan Pemetrexed Irinotecan Capecitabine Marimastat Tegafur/uracil Tipifarnib	Gem	22	5886	2932	2954	12-month OS	RR	0.96	0.93	0.98	Fixed	Critically low	NA	NA	NA	VS	S	No	No	Very Low
A. S. Sultana 2007 [31]	Advanced PC	Combination Treatment Cisplatin Tegafur/uracil 5FU 5FU/FA Capecitabine Oxaliplatin Gem/ Cisplatin/5FU/ Epirubicin Irinotecan Pemetrexed Exatecan	Gem	19	4697	2331	2366	OS	HR	0.91	0.85	0.97	Fixed	Low	NA	NS	2.60%	VS	NS	Yes	No	Very Low
V. B. Heinemann 2008 [33]	Advanced PC [PS 0]	Gem/Cytotoxic Pemetrexed Irinotecan Exatecan	Gem	5	1108	554	554	OS	HR	0.76	0.67	0.87	Fixed	Low	S	NS	0%	S	NS	No	No	Low

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Petrelli F 2014 [38]	Advanced PC	Combination Treatment 5FU Cisplatin Capecitabine Irinotecan Tegafur/uracil Oxaliplatin Gem/ Cisplatin/5FU/ Epirubicin 5FU/FA Pemetrexed Exatecan FOLFIRINOX Liposomal paclitaxel S-1 Gem/Nab	Gem	24	8421	NA	439	OS	HR	0.87	0.81	0.93	Random	Low	NA	S	38%	VS	NS	No	No	Very Low
Cao C 2015 [27]	Advanced PC [Asian]	Gem/S-1	Gem	4	878	432	NA	OS	HR	0.82	0.70	0.96	Fixed	Critically low	NA	NS	0%	NS	NS	No	No	NA
Liu Y 2015 [40]	Advanced PC	Gem/S-1	Gem	4	917	458	459	OS	HR	0.83	0.72	0.96	Fixed	Low	S	NS	0%	NS	NS	No	No	Moderate
Tu C 2015 [19]	Advanced PC	Gem Combination Gem/5FU Gem/Cap Gem/S-1	Gem	12	3038	NA	NA	OS	HR	0.88	0.81	0.95	Fixed	Critically low	NA	NS	0%	VS	NS	No	No	Low
Jin SF 2017 [28]	Advanced PC	Gem Combination Cisplatin S-1	Gem	8	1619	805	814	OS	HR	0.85	0.76	0.95	Fixed	Critically low	NA	NS	0%	S	NS	NA	No	NA
Zhang XW 2017 [26]	Advanced PC	Gem/ Fluropyrimidine 5FU Capecitabine S-1 Tegafur/uracil	Gem	11	2800	NA	NA	OS	HR	0.86	0.79	0.93	Fixed	Moderate	NA	NS	0%	VS	NS	No	No	NA
Zhang XW 2017 [26]	Advanced PC	Gem/Taxanes GemNab Liposomal paclitaxel Docetaxel	Gem	5	1314	NA	NA	OS	HR	0.75	0.67	0.85	Fixed	Moderate	S	NS	11.20%	NS	NS	No	No	Moderate

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Zhang XW 2017 [26]	Advanced PC	Combination Treatment 5FU Capecitabine S-1 Tegafur/uracil Cisplatin Oxaliplatin GemNab Liposomal paclitaxel Docetaxel Irinotecan exatecan Pemetrexed	Gem	24	7148	NA	NA	OS	HR	0.89	0.85	0.94	Fixed	Moderate	NA	NS	16.20%	VS	NS	No	No	Low
Lin KI 2019 [37]	Advanced PC	Gem/ Fluropyrimidine Capecitabine S-1	Gem	5	1898	1087	811	OS	HR	0.86	0.78	0.95	Random	High	S	NS	0%	NS	NS	No	No	Moderate
Lin KI 2019 [37]	Advanced PC	Gem/Taxanes GemNab Liposomal paclitaxel	Gem	2	961	481	480	OS	HR	0.71	0.62	0.82	Random	High	S	NS	0%	NS	NS	NA	No	Moderate
Xiao BY 2020 [24]	Advanced PC	Gem/Cap	Gem	3	1581	534	532	OS	HR	0.85	0.75	0.95	Fixed	Moderate	S	NS	0%	NS	NS	No	No	Moderate
Kharat 2021 [22]	Advanced PC	Combination Treatment Gem/Cap Gem/Nab FOLFIRINOX	Gem	6	2089	1043	1046	OS	HR	0.76	0.68	0.85	Random	Moderate	NS	NS	56%	NS	NS	No	No	Moderate
E. M. Bria 2007 [29]	Advanced PC	Combination Treatment Cisplatin Tegafur/uracil Gem/ Cisplatin/5FU/ Epirubicin Oxaliplatin 5FU 5FU/FA Capecitabine Irinotecan Pemetrexed Exatecan Marimastat Erlotinib	Gem	20	6296	NA	NA	PFS	RR	0.91	0.84	0.98	Fixed/ random	Critically low	NA	NA	NA	S	NS	No	NA	NA
E. M. Bria 2007 [29]	Advanced PC	Gem Platinum Cisplatin Oxaliplatin Gem/ Cisplatin/5FU/ Epirubicin	Gem	7	1354	NA	NA	PFS	RR	0.67	0.53	0.83	Fixed/ random	Critically low	NA	NA	NA	S	NS	No	NA	NA
Cao C 2015 [27]	Advanced PC [Asian]	Gem/S-1	Gem	4	878	432	439	PFS	HR	0.64	0.55	0.74	Fixed	Critically low	NA	NS	0%	NS	NS	No	No	NA

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Liu Y 2015 [40]	Advanced PC	Gem/S-1	Gem	4	917	458	459	PFS	HR	0.64	0.56	0.74	Fixed	Low	S	NS	0%	NS	NS	No	No	Moderate
Tu C 2015 [19]	Advanced PC	Gem Combination Gem/5FU Gem/Cap gem/S-1	Gem	8	2130	NA	NA	PFS	HR	0.74	0.63	0.86	Random	Critically low	NA	S	54.50%	S	NS	No	No	Low
Huang D 2016 [32]	Advanced PC	Gem/Cisplatin	Gem	3	502	205	297	PFS	OR	2.11	1.43	3.11	Fixed	Low	NA	NS	0%	NS	NS	NA	Yes	NA
Jin SF 2017 [21]	Advanced PC	Gem Combination Cisplatin S-1	Gem	8	1507	752	755	PFS	HR	0.76	0.65	0.90	Random	Critically low	NA	S	51%	S	NS	NA	No	Low
Zhang XW 2017 [26]	Advanced PC	Gem/ Fluropyrimidine 5FU Capecitabine S-1 Tegafur/uracil	Gem	8	2135	NA	NA	PFS	HR	0.71	0.64	0.78	Fixed	Moderate	NA	NS	10.40%	S	NS	No	No	NA
Zhang XW 2017 [26]	Advanced PC	Combination Treatment 5FU Capecitabine S-1 Tegafur/uracil Cisplatin Oxaliplatin GemNab Liposomal paclitaxel Docetaxel Irinotecan Exatecan	Gem	19	NA	NA	NA	PFS	HR	0.80	0.73	0.88	Random	Moderate	NA	S	66.30%	VS	NS	No	No	Very Low
Lin KI 2019 [37]	Advanced PC	Gem/ Fluropyrimidine Capecitabine S-1	Gem	4	1402	702	700	PFS	HR	0.75	0.65	0.86	Random	High	S	S	46%	NS	NS	No	No	Low
Lin KI 2019 [37]	Advanced PC	Gem/Taxanes Gem/Nab Liposomal paclitaxel	Gem	2	961	481	480	PFS	HR	0.79	0.59	0.82	Random	High	S	NS	0%	NS	NS	NA	No	Moderate
Xiao BY 2020 [24]	Advanced PC	Gem/Cap	Gem	3	1581	534	532	PFS	HR	0.80	0.72	0.90	Fixed	Moderate	S	NS	0%	S	NS	No	No	Moderate
Kharat 2021 [22]	Advanced PC	Combination Treatment Gem/Cap Gem/Nab FOLFIRINOX	Gem	6	2089	1043	1046	PFS	HR	0.68	0.60	0.78	Random	Moderate	NS	S	65%	NS	NS	No	No	Moderate

PC: pancreatic cancer; OS: overall survival; PFS: progression free survival; DFS: disease free survival; HR: hazard ratio; RR: risk ratio; SS: sample size; LCI : lower confidence interval; UCI: upper confidence interval; ROB: risk of bias; GRADE: Grading of recommendations, assessment,
Development and evaluations; VS: very serious; S: serious; NS: not serious; NA: not applicable; Gem: gemcitabine; Gem/Cap: gemcitabine capecitabine; Gem/Nab: gemcitabine nab-paclitaxel; Gem/S-1: gemcitabine S-1; 5FU: 5-fluorouracil; FU: fluorouracil; FA: folinic acid.

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quality of evidence is categorized as very low, low, moderate, and high [14]. GRADEpro version 3.6.1. was used for assessing strength of evidence (McMaster University, 2014).

For each meta-analysis that was initially graded as high or moderate quality of evidence, a series of sensitivity analyses were performed to determine the robustness of the findings as follows: excluding primary studies with a high risk of bias and by excluding small-sized studies (i.e., include 25% of the largest trials and exclude small sized studies regardless of existence of small study effect) [15,16].

Results

Study selection

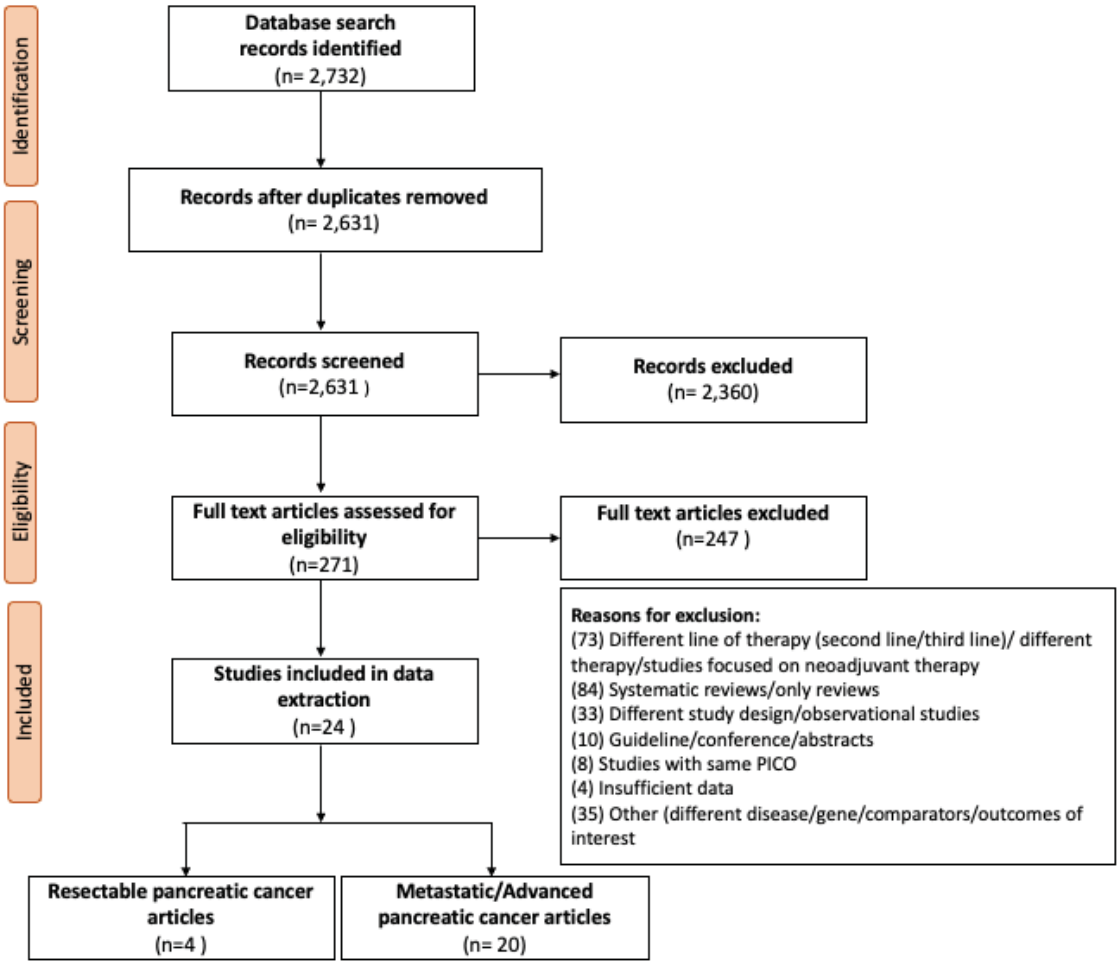
A total of 2,732 publication were screened and of those 271 (9.92%) full-text articles were assessed for eligibility. From 271 articles, 24 (8.85%) [17-40] articles corresponding to 168 meta-analyses in patients with either resected (n = 34) or metastatic (n = 134) PCs were included in this umbrella review (Figure 1). The reasons for exclusion for the remaining 247 (91.15%) articles are provided in supplementary material (eTable 3).

Study characteristics

Characteristics of the included meta-analyses are summarized in supplementary material (eTable 4, eTable 5). The median number of RCTs per meta-analysis for both survival and adverse event outcomes were 5 [Interquartile range (IQR): survival outcome (3-7); adverse event outcomes (4-9)]. The sample size per meta-analysis was 1043 for survival outcomes (IQR: 468 – 2089) and 1442 for adverse event outcomes (IQR: 916 – 2104). The median duration of follow up time was 41 months (IQR: 34 – 57). The meta-analyses included in this umbrella review were published between 2006 and 2021. Among 168 meta-analyses, 80 (47.61%) and 88 (52.38%) meta-analyses reported survival and adverse event outcomes, respectively.

Quality assessment

Evaluation of methodological quality of included meta-analyses using AMSTAR-2 revealed that only 2 (8%) [36,37] studies were found to be of high methodological quality, 6 (25%) [17,21,24-26] were moderate, 9 (38%) [18,20,30-33,38-40] were low, and the remaining 7 (29%) [19,23,27–29,34,35] were rated as critically low quality.



PICO – population, intervention, comparator, and outcome.

Figure 1: Study flow diagram.

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Findings from survival outcomes

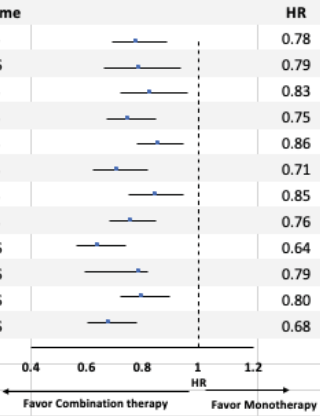
Among 80 meta-analyses, OS was reported in 56 (resected – 5; metastatic – 51) meta-analyses and the remaining 24 (resected – 7; metastatic – 17) reported PFS. A total of 36 meta-analyses (45%) were found to be statistically significant at p ≤0.05 [resected: OS – 3, PFS – 4; metastatic: OS – 16, PFS – 13] (Descriptive characteristics of all statistically significant associations for survival outcomes are included in Table 1). Overall, the findings from these meta-analyses suggested that the combination treatment regimens improved survival outcomes compared to gemcitabine monotherapy. Combination treatments reported a median survival of 16.8 months (IQR: 5 -23) compared to 9.3 months (IQR: 3 – 14) for gemcitabine monotherapy. Forty-four (55%) meta-analyses were found to be non-statistically significant and the descriptive characteristics of survival outcomes without statistical significance at p≤0.05 are presented in eTable 4.

GRADE was used to assess strength of evidence and we found that majority of the meta-analyses were graded as either low (N = 28) or very low (N = 22) quality. Twelve meta-analyses focusing on survival outcomes were found to be of moderate quality (Figure 2). We were unable to grade 18 meta-analyses because of lack of either risk of bias data or publication bias data. Among 12 meta-analyses [22,24,26,36,37,40] graded as moderate quality, 2 meta-analyses [22,36] comparing combination therapy (gem/cap, FOLFIRINOX, and gem/nab) with gemcitabine monotherapy demonstrated improved OS (HR=0.78 (0.69-0.89)) and PFS (HR=0.79 (0.66-0.94)) in resected PC patients. Improvements in PFS for resected PC was specific for R0 resection cases whereas OS was applicable to both patients with R0 and R1 resection. Other 6 meta-analyses [22,24,26,37,40] comparing combination therapy with gemcitabine monotherapy demonstrated improved OS in metastatic PC patients (Figure 2). Gem/taxane combinations [nab-paclitaxel and liposomal paclitaxel (HR = 0.71 (0.62-0.82)) and nab-paclitaxel, liposomal paclitaxel, and docetaxel (HR = 0.75 (0.67-0.85))] followed by combination of gem/cap, gem/nab, and FOLFIRINOX (HR = 0.76(0.68-0.85)) were found to have the highest OS improvement. The remaining 4 meta-analyses [22,24,37,40] comparing combination therapy with gemcitabine monotherapy demonstrated improved PFS among metastatic PC patients (Figure 2). Gem/S-1 was found to have the highest PFS with a HR of 0.64 (0.56 – 0.74), followed by gem/cap, gem/nab and FOLFIRINOX (HR = 0.68 (0.60 -0.78)). Gemcitabine combinations with taxanes and capecitabine showed modest improvements in PFS (gem/taxanes: HR = 0.79 (0.59-0.82); gem/cap: HR = 0.80 (0.72-0.90)).

Findings from safety outcomes

Of the 88 meta-analyses reporting adverse event outcomes, 22 were for resected PC and 66 for metastatic PC. The most common adverse events included in meta-analyses were nausea/vomiting (N = 17), neutropenia (N = 16), anemia (N = 13), diarrhea (N = 13), thrombocytopenia (N = 12), fatigue (N = 8), leukopenia (N = 4), neuropathy (N = 1), and combination of different above adverse events (N = 4). Of the 88 meta-analyses, 42 (47.72%) were found to be statistically significant at p≤0.05 (Descriptive characteristics of all statistically significant associations for safety outcomes are included in Table 2). List of statistically significant AEs were as follows: diarrhea (N = 9), neutropenia (N = 8), thrombocytopenia (N = 7), nausea/vomiting (N = 6), fatigue (N = 3), leukopenia (N = 2), anemia (N = 2), neuropathy (N = 1), and combination of different above adverse events (N = 4). Of the 42 meta-analysis that were found to be statistically significant, 32 (76.19%) meta-analysis suggested that combination treatment regimens were associated with increased risk of adverse events among both resected and metastatic PC compared to gemcitabine monotherapy. The remaining 10 (23.81%) meta-analyses suggested that combination regimens did not significantly increase risk of adverse events, specifically neutropenia (metastatic PC – 2; resected PC - 1), thrombocytopenia (metastatic PC – 1; resected PC - 1), followed by anemia (n = 1), leukopenia (n= 1) for resected PC, and nausea/vomiting (n = 2) and diarrhea (n =1) for metastatic PC (Table 2). The remaining 46 (52.27%) meta-analyses were found to be non-statistically significant and the descriptive characteristics of

Author	Population	Combination intervention	Comparartor	Outcome	HR	95% CI		I^2 (%)	AMSTAR
Kharat et al., 2021	Resected	Gem/Cap, Gem/Nab, FOL	Gem	OS	0.78	0.69	0.89	13	Moderate
Galvano et al., 2020	R0 Resected	Gem/Cap, Gem/Nab, FOL	Gem	DFS	0.79	0.66	0.94	20	High
Liu et al., 2015	Advanced PC	Gem/S-1	Gem	OS	0.83	0.72	0.96	0	Low
Zhang et al., 2017	Advanced PC	Gem/Nab, Liposomal PXL, Docetaxel	Gem	OS	0.75	0.67	0.85	11	Moderate
Lin et al., 2019	Advanced PC	Gem/Cap, Gem/S-1	Gem	OS	0.86	0.78	0.95	0	High
Lin et al., 2019	Advanced PC	Gem/Nab, Liposomal PXL	Gem	OS	0.71	0.62	0.82	0	High
Xiao et al., 2020	Advanced PC	Gem/Cap	Gem	OS	0.85	0.75	0.95	0	Moderate
Kharat et al., 2021	Advanced PC	Gem/Cap, Gem/Nab, FOL	Gem	OS	0.76	0.68	0.85	56	Moderate
Liu et al., 2015	Advanced PC	Gem/S-1	Gem	PFS	0.64	0.56	0.74	0	Low
Lin et al., 2019	Advanced PC	Gem/Nab, Liposomal PXL	Gem	PFS	0.79	0.59	0.82	0	High
Xiao et al., 2020	Advanced PC	Gem/Cap	Gem	PFS	0.80	0.72	0.90	0	Moderate
Kharat et al., 2021	Advanced PC	Gem/Cap, Gem/Nab, FOL	Gem	PFS	0.68	0.60	0.78	65	Moderate



OS – overall survival; PFS – progression free survival; DFS – disease free survival; HR – hazard ratio; CI – confidence interval; Gem/Cap – gemcitabine capecitabine; Gem/Nab – gemcitabine nab-paclitaxel; FOL – FOLFIRINOX; Gem/S-1 – gemcitabine S-1; Liposomal PXL – liposomal paclitaxel; PC – pancreatic cancer

Figure 2: Figure describing study characteristics of moderate quality meta-analyses.
OS: overall survival; PFS: progression free survival; DFS: disease free survival; HR: hazard ratio; CI: confidence interval; Gem/Cap: gemcitabine capecitabine; Gem/Nab; gemcitabine nab-paclitaxel; FOL: FOLFIRINOX; Gem/S-1: gemcitabine S-1; Liposomal PXL: liposomal paclitaxel; PC: pancreatic cancer

Citation: Kharat A, Tan CJ, Saeteaw M, Chhibber A, Chaiyakunapruk N, et al. (2022) Survival benefits and safety of chemotherapy regimens for pancreatic cancer: An umbrella review of meta-analyses of randomized controlled trials. Ann Pancreat Disord Treatm 4(1): 001-020. DOI: https://dx.doi.org/10.17352/apdt.000008

Table 2: Descriptive characteristics of statistically significant studies included for safety outcomes.

First Author	Population	Intervention	Com-parator	Outcome	No of studies	Total			Combination Therapy			Single Agent			Model						AMSTAR	GRADE							Final GRADE evaluation
						Events	Total	%	Events	Total	%	Events	Total	%	Random/ fixed	effect metric	effect size	LCI	UCI	p - value		ROB	Inco-nsi-stency	I2 value [%]	Indir-ectness	Impre-cision	Publi-cation Bias [yes, no]	Large effect	
Neutropenia/Febrile Neutropenia																													
H. H. Chen 2018 [35]	Resected PC	S-1	Gem	Neutropenia	2	164	434	38	NA	NA	NA	NA	NA	NA	Random	RR	0.26	0.15	0.44	<0.001	Critically Low	S	NA	NR	NS	NS	No	Yes	NA
D. B. Ciliberto 2012 [39]	Advanced PC	Gem/ Fluropyrimidine 5FU Capecitabine S-1 5FU/FA Tegafur/uracil Gem Platinum Cisplatin Oxaliplatin Gem/Targeted Tipifarnib Erlotinib Bevacizumab Cetuximab Axitinib Marimastat Gem/Irinotecan Gem/Cisplatin Gem/Oxaliplatin Gem/Irinotecan Gem/Cisplatin Gem/Oxaliplatin	vGem	Neutropenia	34	NA	NA	NA	NA	NA	NA	NA	NA	NA	Random	RR	0.71	0.59	0.85	<0.001	Low	S	NA	NR	VS	vNS	No	No	Very Low
C. A. Sun 2012 [23]	Advanced PC	Gem/ Fluropyrimidine 5FU Capecitabine	Gem	Neutropenia	5	235	1298	18	139	649	21	96	649	15	Random	RR	0.7	0.55	0.88	NA	Critically low	S	NS	0	S	NS	No	No	Low
Li Q 2014 [25]	Advanced PC	Gem Combination Gem/Cap gem/S-1 Gem/5FU	Gem	Neutropenia	7	588	1963	30	350	979	36	238	984	24	Fixed	OR	1.9	1.54	2.34	<0.01	Moderate	S	S	46	NS	NS	NA	No	Low
Liu Y 2015 [40]	Advanced PC	Gem/S-1	Gem	Neutropenia	4	386	876	44	234	NA	53.55	152	NA	34	Random	RR	1.6	1.14	2.25	0.007	Low	S	NA	NR	NS	NS	No	No	NA
Jin SF 2017 [21]	Advanced PC	Gem Combination Cisplatin S-1	Gem	Neutropenia	7	478	697	69	293	679	43	185	697	27	Fixed	RR	1.62	1.41	1.87	<0.001	Critically low	NA	NS	25	S	NS	NA	No	NA

Citation: Kharat A, Tan CJ, Saeteaw M, Chhibber A, Chaiyakunapruk N, et al. (2022) Survival benefits and safety of chemotherapy regimens for pancreatic cancer: An umbrella review of meta-analyses of randomized controlled trials. Ann Pancreat Disord Treatm 4(1): 001-020. DOI: https://dx.doi.org/10.17352/apdt.000008

Zhang XW 2017 [26]	Advanced PC	Gem/ Fluropyrimidine 5FU Capecitabine S-1 Tegafur/uracil	Gem	Neutropenia	11	NA	2720	NA	NA	NA	NA	NA	NA	NA	Random	RR	1.52	1.37	1.68	<0.001	Moderate	NA	NA	NR	S	NS	No	No	NA
Zhang XW 2017 [26]	Advanced PC	Combination Treatment 5FU Capecitabine S-1 Tegafur/uracil Cisplatin Oxaliplatin GemNab Liposomal paclitaxel Docetaxel Irinotecan Exatecan Pemetrexed	Gem	Neutropenia	26	NA	7200	NA	NA	NA	NA	NA	NA	NA	Random	RR	1.35	1.17	1.57	<0.001	Moderate	NA	NA	NR	VS	NS	No	No	Low
Thrombocytopenia																													
H. H. Chen 2018 [35]	Resected PC	S-1	Gem	Thromb-ocytopenia	2	31	434	7	NA	NA	NA	NA	NA	NA	Random	RR	0.43	0.2	0.89	0.02	Critically Low	S	NA	NR	NS	NS	No	Yes	NA
D. B. Ciliberto 2012 [39]	Advanced PC	Gem/ Fluropyrimidine 5FU Capecitabine S-1 5FU/FA Tegafur/uracil Gem Platinum Cisplatin Oxaliplatin Gem/Targeted Tipifarnib Erlotinib Bevacizumab Cetuximab Axitinib Marimastat Gem/Irinotecan Gem/Cisplatin Gem/Oxaliplatin Gem/Irinotecan Gem/Cisplatin Gem/Oxaliplatin	Gem	Thrombo-cytopenia	34	NA	NA	NA	NA	NA	NA	NA	NA	NA	Random	RR	0.57	0.43	0.75	<0.001	Low	S	NA	NR	VS	NS	No	No	Very Low

Citation: Kharat A, Tan CJ, Saeteaw M, Chhibber A, Chaiyakunapruk N, et al. (2022) Survival benefits and safety of chemotherapy regimens for pancreatic cancer: An umbrella review of meta-analyses of randomized controlled trials. Ann Pancreat Disord Treatm 4(1): 001-020. DOI: https://dx.doi.org/10.17352/apdt.000008

Li Q 2014 [25]	Advanced PC	Gem Combination Gem/Cap Gem/S-1 Gem/5FU	Gem	Thrombo-cytopenia	8	202	1300	16	122	267	46	80	1033	8	Fixed	OR	1.62	1.2	2.18	<0.01	Moderate	S	S	28	NS	NS	No	NA	Low
Liu Y 2015 [40]	Advanced PC	Gem/S-1	Gem	Thrombo-cytopenia	5	112	917	12	71	NA	15.5	41	NA	9	Random	RR	1.73	1.21	2.49	0.003	Low	S	NA	NS	S	No	No	No	Low
Jin SF 2017 [21]	Advanced PC	Gem Combination Cisplatin S-1	Gem	Thrombo-cytopenia	9	177	1611	11	110	798	14	67	813	8	Fixed	RR	1.65	1.25	2.2	0.0005	Critically low	NA	S	45	S	NS	No	NA	Low
Zhang XW 2017 [26]	Advanced PC	Gem/ Fluropyrimidine 5FU Capecitabine S-1 Tegafur/uracil	Gem	Thromb-ocytopenia-	11	NA	2720	NA	NA	NA	NA	NA	NA	NA	Random	RR	1.63	1.31	2.03	<0.001	Moderate	NA	NA	NR	S	NS	No	No	NA
Zhang XW 2017 [26]	Advanced PC	Combination Treatment 5FU Capecitabine S-1 Tegafur/uracil Cisplatin Oxaliplatin Gem/Nab Liposomal paclitaxel Docetaxel Irinotecan exatecan Pemetrexed	Gem	Thrombo-cytopenia-	26	NA	7200	NA	NA	NA	NA	NA	NA	NA	Random	RR	1.63	1.28	2.07	<0.001	Moderate	NA	NA	NR	VS	NS	No	No	Low
Leukopenia																															
H. H. Chen 2018 [35]	Resected PC	Gem/S-1	Gem	Leukopenia	2	102	434	24	NA	NA	NA	NA	NA	NA	Random	RR	0.22	0.13	0.35	<0.00001	Critically Low	S	NA	NR	NS	NS	No	Yes	NA
Jin SF 2017 [21]	Advanced PC	Gem Combination Cisplatin S-1	Gem	Leukopenia	8	249	1502	17	162	747	22	87	755	12	Fixed	RR	1.88	1.49	2.37	<0.001	Critically Low	NA	NS	0	S	NS	No	No	NA
Anemia																															
P. Parmar 2020 [18]	Resected PC	Combination Treatment Gem/Nab FOLFIRINOX Gem/Cap S-1	Gem	Anemia	4	246	2435	10	105	1213	9	141	1222	12	Random	RR	0.74	0.59	0.94	NA	Low	NS	NS	0	S	NS	No	NA	NA
Jin SF 2017 [21]	Advanced PC	Gem Combination Cisplatin S-1	Gem	Anemia	9	173	1611	11	101	798	13	72	813	9	Fixed	RR	1.41	1.07	1.88	0.02	Critically Low	NA	NS	0	S	NS	No	No	NA

Citation: Kharat A, Tan CJ, Saeteaw M, Chhibber A, Chaiyakunapruk N, et al. (2022) Survival benefits and safety of chemotherapy regimens for pancreatic cancer: An umbrella review of meta-analyses of randomized controlled trials. Ann Pancreat Disord Treatm 4(1): 001-020. DOI: https://dx.doi.org/10.17352/apdt.000008

Neuropathy																													
A. C. Galvano 2020 [36]	Resected PC	Combination Treatment Gem/Cap Gem/Nab FOLFIRINOX	Gem	Neutropathy	2	86	1334	667	13	0	667	0	Random	RR	76.44	10.65	548.9	NA	High	S	NS	0	NS	VS	NA	Yes	Very Low
Fatigue																													
A. C. Galvano 2020 [36]	Resected PC	Combination Treatment Gem/Cap Gem/Nab FOLFIRINOX	Gem	Fatigue	3	132	2046	1026	9	43	1020	4	Random	RR	2	1.01	3.97	NA	High	S	S	71	NS	NS	No	No	Low
Zhang XW 2017 [26]	Advanced PC	Gem/Taxanes Gem/Nab Liposomal paclitaxel Docetaxel	Gem	Fatigue	2	NA	946	NA	NA	NA	NA	NA	Random	RR	2.26	1.56	3.28	<0.001	Moderate	NA	NA	NR	S	NS	No	No	Low
Zhang XW 2017 [26]	Advanced PC	Combination Treatment 5FU Capecitabine S-1 Tegafur/uracil Cisplatin Oxaliplatin GemNab Liposomal paclitaxel Docetaxel Irinotecan exatecan Pemetrexed	Gem	Fatigue	16	NA	4636	NA	NA	NA	NA	NA	Random	RR	1.38	1.15	1.65	<0.001	Moderate	NA	NA	NR	VS	NS	No	No	Low
Diarrhea																													
H. H. Chen 2018 [35]	Resected PC	Combination Treatment S-1 5FU/FA Gem/Cap Gem/Erlotinib	Gem	Diarrhea	5	39	1166	434	3	NA	2052	5	Random	RR	6.96	1.6	329.29	0.04	Critically Low	S	NA	NR	NS	VS	S	No	Yes	Low
H. H. Chen 2018 [35]	Resected PC	S-1	Gem	Diarrhea	2	9	434	2	NA	NA	NA	NA	Random	RR	19.3	1.13	329.29	0.04	Critically Low	S	NA	NR	NS	VS	S	No	Yes	Very Low
A. C. Galvano 2020 [36]	Resected PC	Combination Treatment Gem/Cap Gem/Nab FOLFIRINOX	Gem	Diarrhea	3	104	2052	1026	8	19	1026	2	Random	RR	4.42	2.71	7.2	NA	High	S	NS	o	NS	S	No	No	Low

Citation: Kharat A, Tan CJ, Saeteaw M, Chhibber A, Chaiyakunapruk N, et al. (2022) Survival benefits and safety of chemotherapy regimens for pancreatic cancer: An umbrella review of meta-analyses of randomized controlled trials. Ann Pancreat Disord Treatm 4(1): 001-020. DOI: https://dx.doi.org/10.17352/apdt.000008

D. B. Ciliberto 2012 [39]	Advanced PC	Gem/ Fluropyrimidine 5FU Capecitabine S-1 5FU/FA Tegafur/uracil Gem Platinum Cisplatin Oxaliplatin Gem/Targeted Tipifarnib Erlotinib Bevacizumab Cetuximab Axitinib Marimastat Gem/Irinotecan Gem/Cisplatin Gem/Oxaliplatin Gem/Irinotecan Gem/Cisplatin Gem/Oxaliplatin	Gem	Diarrhea	34	NA	NA	NA	NA	NA	NA	NA	NA	NA	Random	RR	0.53	0.36	0.79	0.002	Low	S	NA	NR	VS	NS	No	No	Very Low
Li Q 2014 [25]	Advanced PC	Gem Combination Gem/Cap gem/S-1 Gem/5FU	Gem	Diarrhea	7	79	1963	4	53	979	5	26	984	3	Fixed	OR	2.04	1.28	3.26	<0.01	Moderate	S	NS	21	S	NS	NA	No	Low
Liu Y 2015 [40]	Advanced PC	Gem/S-1	Gem	Diarrhea	4	21	876	2	16	NA	3.66	5	NA	1.14	Random	RR	2.84	1.13	7.13	0.03	Low	S	NA	NR	NS	NS	No	No	NA
Zhang XW 2017 [26]	Advanced PC	Gem/ Fluropyrimidine 5FU Capecitabine S-1 Tegafur/uracil	Gem	Diarrhea	11	NA	2720	NA	NA	NA	NA	NA	NA	NA	Random	RR	2.29	1.5	3.48	<0.001	Moderate	NA	NA	NR	VS	NS	No	No	Low
Zhang XW 2017 [26]	Advanced PC	Gem/Taxanes Gem/Nab Liposomal paclitaxel	Gem	Diarrhea	2	NA	946	NA	NA	NA	NA	NA	NA	NA	Random	RR	6.83	2.42	19.23	<0.001	Moderate	NA	NA	NR	NS	NS	No	Yes	NA
Zhang XW 2017 [26]	Advanced PC	Combination Treatment 5FU Capecitabine S-1 Tegafur/uracil Cisplatin Oxaliplatin Gem/Nab Liposomal paclitaxel Docetaxel Irinotecan Exatecan Pemetrexed	Gem	Diarrhea	23	NA	6807	NA	NA	NA	NA	NA	NA	NA	Random	RR	2.51	1.85	3.39	<0.001	Moderate	NA	NA	NR	VS	NS	No	No	Low
Nausea/Vomitting																													

Citation: Kharat A, Tan CJ, Saeteaw M, Chhibber A, Chaiyakunapruk N, et al. (2022) Survival benefits and safety of chemotherapy regimens for pancreatic cancer: An umbrella review of meta-analyses of randomized controlled trials. Ann Pancreat Disord Treatm 4(1): 001-020. DOI: https://dx.doi.org/10.17352/apdt.000008

D. B. Ciliberto 2012 [39]	Advanced PC	Gem/ Fluropyrimidine 5FU Capecitabine S-1 5FU/FA Tegafur/uracil Gem Platinum Cisplatin Oxaliplatin Gem/Targeted Tipifarnib Erlotinib Bevacizumab Cetuximab Axitinib Marimastat Gem/Irinotecan Gem/Cisplatin Gem/Oxaliplatin Gem/Irinotecan Gem/Cisplatin Gem/Oxaliplatin	Gem	Nausea	34	NA	NA	NA	NA	NA	NA	NA	NA	NA	Random	RR	0.74	0.56	0.96	0.026	Moderate	S	NA	NR	VS	NS	No	No	Very Low
C. A. Sun 2012 [23]	Advanced PC	Gem Platinum Cisplatin Oxaliplatin	Gem	Vomiting	6	145	1617	9	100	811	12	45	806	6	Random	RR	0.46	0.33	0.64	NA	Critically low	S	NS	20	S	NS	No	No	Low
Liu Y 2015 [40]	Advanced PC	Gem/S-1	Gem	Nausea/ Vomiting	5	47	917	5	34	NA	7.42	13	NA	2.83	Random	RR	2.84	1.13	7.13	0.03	Low	S	NA	NR	NS	NS	No	No	NA
Zhang XW 2017 [26]	Advanced PC	Gem Platinum Cisplatin Oxaliplatin	Gem	Nausea	4	NA	736	NA	NA	NA	NA	NA	NA	NA	Random	RR	2.57	1.49	4.43	0.001	Moderate	NA	NA	NR	NS	NS	No	No	NA
Zhang XW 2017 [26]	Advanced PC	Combination Treatment 5FU Capecitabine S-1 Tegafur/uracil Cisplatin Oxaliplatin GemNab Liposomal paclitaxel Docetaxel Irinotecan Exatecan Pemetrexed	Gem	Nausea	16	NA	4583	NA	NA	NA	NA	NA	NA	NA	Random	RR	1.61	1.31	1.97	<0.001	Moderate	NA	NA	NR	VS	NS	No	No	Low

Citation: Kharat A, Tan CJ, Saeteaw M, Chhibber A, Chaiyakunapruk N, et al. (2022) Survival benefits and safety of chemotherapy regimens for pancreatic cancer: An umbrella review of meta-analyses of randomized controlled trials. Ann Pancreat Disord Treatm 4(1): 001-020. DOI: https://dx.doi.org/10.17352/apdt.000008

Zhang XW 2017 [26]	Advanced PC	Combination Treatment 5FU Capecitabine S-1 Tegafur/uracil Cisplatin Oxaliplatin GemNab Liposomal paclitaxel Docetaxel Irinotecan Exatecan Pemetrexed	Gem	Vomiting	16	NA	4627	NA	NA	NA	NA	NA	NA	NA	Random	RR	1.45	1.11	1.89	0.007	Moderate	NA	NA	NR	VS	S	No	No	Very Low
Combined adverse events																													
A. C. Galvano 2020 [36]	Resected PC	Combination Treatment Gem/Cap Gem/Nab FOLFIRINOX	Gem	Combined AE Neutropenia Anemia Fatigue Diarrhea Neuropathy	3	2394	14156	17	1458	7075	21	936	7081	13	Random	RR	1.68	1.38	2.05	<0.0001	High	S	VS	82	NS	NS	No	No	Very Low
Kharat 2021 [22]	Resected PC	Combination Treatment Gem/Cap Gem/Nab FOLFIRINOX	Gem	Combined AE Neutropenia Anemia Fatigue Diarrhea	3	572	2089	27	357	1043	34	215	1046	21	Random	RR	1.8	1.02	3.16	NA	Moderate	NS	NS	6.3	NS	S	Yes	No	Low
Jin SF 2017 [28]	Advanced PC	Gem Combination Gem/Cisplatin Gem/S-1	Gem	Combined AE Neutropenia Thrombocytopenia Leukopenia Anemia Anorexia Nausea/Vomiting Diarrhea/ constipation	9	1282	10404	12	800	5153	16	482	5251	9	Fixed	RR	1.68	1.52	1.86	<0.0001	Critically Low	NA	NS	6	S	NS	NA	No	NA
Kharat 2021 [22]	Advanced PC	Combination Treatment Gem/Cap Gem/Nab FOLFIRINOX	Gem	Combined AE Neutropenia Anemia Fatigue Diarrhea	6	1067	4586	23	662	1564	42	405	3022	13	Random	RR	1.47	1.18	1.82	NA	Moderate	S	NS	14.1	S	NS	No	No	Low

PC: pancreatic cancer; OS: overall survival; PFS: progression free survival; DFS: disease free survival; HR: hazard ratio; RR: risk ratio; SS: sample size, LCI: lower confidence interval; UCI: upper confidence interval; ROB: risk of bias, GRADE: Grading of recommendations, assessment,
development, and evaluations; VS: very serious; S: serious; NS: Not serious; NA: not applicable; NR: not reported; Gem: gemcitabine; Gem/Cap: gemcitabine capecitabine; Gem/Nab: gemcitabine nab-paclitaxel; Gem/S-1: gemcitabine S-1; 5FU: 5- fluorouracil, FU: fluorouracil, FA: folinic acid.

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safety outcomes without statistical significance at p≤0.05 are presented in eTable 5.

We found that majority of the meta-analyses were graded as either low (N=36) or very low (N=30) quality. No meta-analysis for adverse events was found to be of moderate or high quality. We could not grade 22 meta-analyses, and this was due to lack of either risk of bias data or publication bias data (eTable 5).

Sensitivity analysis

Findings from sensitivity analyses are presented in supplementary material eTable 6. When RCTs with a high risk of bias were excluded, only one meta-analysis [24] comparing gem/cap to gemcitabine monotherapy for PFS in patients with metastatic PC was downgraded to low quality due to imprecision, while others retained the same rank. A sensitivity analysis excluding small-sized studies showed that one meta-analysis [22] comparing gemcitabine combination therapy (with nab/paclitaxel or capecitabine) versus gemcitabine monotherapy among metastatic PC patients for PFS was upgraded to high quality evidence (HR = 0.78 (95%CI, 0.69-0.88)). Meanwhile, one meta-analysis [26] comparing gem/taxanes (nab-paclitaxel, liposomal paclitaxel, and docetaxel) to gemcitabine monotherapy was downgraded to very low quality because of high imprecision, while others retained the same rank.

Discussions

Chemotherapy is one of the most effective modalities to improve outcomes in PC treatment. Chemotherapeutic agents, such as fluorouracil and gemcitabine, have been used both as monotherapy and in combination with other drugs for PC. With more clinical studies performed, the efficacy and safety of numerous chemotherapy regimens have been gradually improved over the years and are often individualized to patient characteristics. Several meta-analyses have compiled clinical studies to compare clinical outcomes of chemotherapy regimens. However, no attempt has been made to summarize the overall findings from these meta-analyses and assess the quality of evidence. To our understanding, this is the first umbrella review performed to include the most recent evidence on chemotherapy treatments in both resected and metastatic PC exploring efficacy and safety outcomes.

Our findings suggest that there were only 2 of 24 studies of high methodological quality using the AMSTAR-2 tool and 12 of 168 meta-analyses of moderate strength of evidence using GRADE. This shows that majority of the existing evidence is of poor quality, and we need additional studies with high quality to be published. In addition, most meta-analyses were focused on metastatic PC. There were only 34 of 168 meta-analyses that explored outcomes in resected PC. The clinical studies focused on resected PC are limited and we need more investigative studies focusing on safety and efficacy of adjuvant chemotherapy treatments.

Conventionally, combining different chemotherapeutic agents for antineoplastic treatment, especially those with synergistic effects, is expected to enhance the kill rate of cancer cells beyond an additive impact [41]. This could explain the findings of our analysis where combination treatment regimens conferred better survival outcomes in both resected PC and metastatic PC over monotherapy regimens. Recent clinical practice guidelines, including those by the National Comprehensive Cancer Network (NCCN) [5] and the American Society of Clinical Oncology (ASCO) [42,43] recommended combination chemotherapy, such as gemcitabine-based chemotherapy or FOLFIRINOX, as the preferred chemotherapy regimens for resected PC and metastatic PC. For resectable PC, PRODIGE trial comparing FOLFIRINOX to gemcitabine alone found the median overall survival associated with FOLFIRINOX to be 54.4 months, compared to 35 months for gemcitabine (stratified HR for death, 0.64 (95% CI, 0.48-0.86); p = .003), and the median DFS of 21.6 and 12.8 months for FOLFIRINOX and gemcitabine respectively (HR = 0.58 (95% CI, 0.46-0.73); p < 0.001) [44]. In the metastatic setting, FOLFIRINOX compared to gemcitabine alone (OS: 11.1 vs 6.8 months; PFS: 6.4 vs 3.3. months) was associated with a survival advantage ((OS: HR = 0.57 (95% CI, 0.45-0.73); p < 0.001; (PFS: HR = 0.47 (95% CI, 0.37-0.59); p < 0.001)) [45]. SWOG-1505 study compared perioperative FOLFIRINOX vs gem/nab in patients with resectable PC but no differences in survival was found [46]. To date, FOLFIRINOX and gem/nab have been compared in the perioperative setting but no phase III trials have performed direct head-to-head comparisons for FOLFIRINOX against gemcitabine-based combination treatments in the metastatic setting. More trials with FOLFIRINOX are needed to generate further evidence.

Among the gemcitabine-based combinations, results of this study suggest that gemcitabine with nab-paclitaxel represents the most efficacious option, especially among patients with a good performance status (Eastern Cooperative Oncology Group (ECOG) performance score (PS) of 0 to 1). Our findings align with recommendations made by NCCN and ASCO [42,47], that suggest treatment with Gemzar (gemcitabine) and Abraxane (nab-paclitaxel) is more effective than standard single drug therapy for metastatic PC patients [48]. For PC patients with a high ECOG PS, albumin bound paclitaxel combination with gemcitabine has proven to delay cancer progression and improve survival [42,47]. Gemcitabine belongs to a drug class called antimetabolites, which halts growth of cancer cells after being incorporated in the genetic material of the cells. Nab-paclitaxel is a reformulation of an older drug paclitaxel, where the drug particles are bound to albumin, enhancing the delivery to the tumor, hence increasing the kill rate of cancer cells, and reducing off-site adverse effects. From the studies included in our umbrella review, 2 studies [26,37] reporting 4 meta-analyses for gem/nab vs gemcitabine significantly improved survival among patients, but RCTs assessed in these meta-analyses primarily included less severe patients with an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1 [49,50]. Nevertheless, clinical trials evaluating chemotherapy regimens in PC usually include patient populations that have good performance status [51]. Among patients with poorer performance status, evidence to support specific treatments is sparse but modification of combination regimens or monotherapy is often recommended [51,52].

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When evaluating chemotherapeutic regimens for PC treatment, adverse events are an important issue to consider due to the severity of side effects associated with antineoplastic treatment that can greatly affect the quality of life of patients and have consequences on the treatment, such as dose reduction and treatment discontinuation. While combination chemotherapy may provide higher efficacy due to the synergism of different mechanisms of action, patients may suffer from a wider range and potentially more severe adverse effects. Gemcitabine is one of the backbone chemotherapy agents in PC and myelosuppression chemotherapy induced neutropenia is commonly reported among patient receiving gemcitabine, especially in combination with other chemotherapy. Our study showed a significantly increased risk of adverse events in 34 of 42 meta-analyses of gemcitabine-based combination compared with gemcitabine monotherapy especially in neutropenia and thrombocytopenia. Nevertheless, neutropenia is mostly reversible, and its higher risk associated with gemcitabine combination regimens can be managed with existing treatment guidelines on the monitoring and handling of low blood counts [53-55].

Our umbrella review has several limitations. This umbrella review focused on existing meta-analysis. We found that certain important adverse events such as blood clots, pain, and neurotoxicity were not included in existing meta-analysis, preventing us from making a comprehensive evaluation of safety aspects of chemotherapy treatments. This review did not directly assess the quality or recalculate the effect size along with 95% CI of all primary studies included in each meta-analysis. Instead, we relied on assessments reported by study authors. Because our study was restricted to meta-analysis of RCTs, we could not report real-world effectiveness of these chemotherapy treatments. Differences in baseline characteristics of participants in the individualized clinical studies could influence efficacy and safety outcomes comparison. The focus of our review was to provide an overview of safety and efficacy evidence for various chemotherapy treatments from existing meta-analysis, and therefore, we could not analyze interventions by subgroups such as sex, performance status, resection type, and duration of PC.

Conclusion

The use of combination treatment regimens demonstrated survival benefits over gemcitabine monotherapy, but it was also associated with higher adverse events. Gem/taxanes showed high survival benefits for OS but only a modest benefit for PFS for metastatic PC. Combination of FOLFIRINOX, gem/nab, and gem/cap compared to gemcitabine monotherapy was particularly beneficial for both OS and PFS among resected PC patients. In future, head-to-head clinical trials comparing safety and efficacy for FOLFIRINOX vs gemcitabine-based combinations regimens (specifically gem/nab, gem/cap, and gem/cisplatin) are required.

Statement of ethics

This paper is exempt from ethical committee approval because only previously published data from peer reviewed publications was used. These data do not contain any information that could identify subjects.

Author contributions

All authors have equal contribution towards conceptualizing and designing the study. Aditi Kharat, Chia Jie Tan, Manit Saeteaw, and Anindit Chhibber were involved in screening the articles, collecting, and analyzing data. Sajesh Veettil, Joseph Biskupiak, and Nathorn Chaiyakunapruk supervised the project and critically reviewed the study. All authors have read and approved the final article.

Data availability: Data from previously published meta-analyses was used for this study. All data generated or analyzed during this study are included in this article. Further enquiries can be directed to Dr. Chaiyakunapruk.

(**SUPPLEMENTARY MATERIALS**)

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