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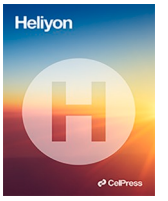

Review article

Efficacy and safety of first-line chemotherapies for patients with advanced pancreatic ductal adenocarcinoma: A systematic review and network meta-analysis

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ABSTRACT

Background: Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease, often diagnosed at an advanced stage. Systemic chemotherapy is the primary treatment, but direct comparisons of different regimens are limited. This study conducted a systematic review and network meta-analysis (NMA) to compare the efficacy and safety of various chemotherapy regimens, with the unique advantage of only including Phase III randomized controlled trials (RCTs).

Methods: NMA was conducted regarding the searched phase III RCTs by comparing overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and adverse events (AEs) of different chemotherapy protocols.

Results: The analysis included 24 studies with 11470 patients across 25 treatment modalities. Among the chemotherapy regimens evaluated, FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) demonstrated the highest OS and PFS, with a risk ratio (logHR) of 4.5 (95 % confidence interval 4.32–4.68) compared to gemcitabine monotherapy. The PEFG regimen (cisplatin, epirubicin, 5-fluorouracil, and gemcitabine) exhibited the highest ORR, with an odds ratio (OR) of 6.67 (2.08–20) compared to gemcitabine monotherapy. Notably, gemcitabine plus sorafenib was associated with the lowest hematological toxicity, with an odds ratio (OR) of 0.1 (0.02–0.48).

Conclusion: Combination therapies may offer greater benefits but also cause more toxic effects. However, combinations with targeted agents seem to have fewer adverse reactions.

1. Introduction

Pancreatic cancer (PC) remains one of the most challenging malignancies in the field of oncology, with the lowest 5-year overall survival (OS) rate among prevalent solid tumors, estimated at approximately 10 % [1]. The predominance of pancreatic ductal adenocarcinoma (PDAC), which accounts for over 90 % of all pancreatic cancer cases, contributes significantly to the dismal prognosis of this disease [2]. PDAC's propensity for late-stage diagnosis exacerbates the difficulty in treatment and adversely impacts patient outcomes.

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Systemic chemotherapy remains the cornerstone of treatment for advanced PDAC [1,3], with FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) and GEM + NPTX (gemcitabine and albumin-bound paclitaxel) representing the standard first-line therapies [1,3,4]. Despite the efficacy of these regimens in prolonging survival and improving quality of life, their use is often limited by significant side effects and the ongoing debate over the optimal balance between therapeutic benefits and toxicity.

A comprehensive review of the literature reveals that while substantial progress has been made in understanding PDAC's molecular underpinnings and clinical behavior [5,6], there remains a notable gap in comparative effectiveness research for chemotherapy regimens. Studies to date have explored various combinations of chemotherapeutic agents, including oxaliplatin, cetuximab, and newer targeted therapies [4]. However, direct comparisons between these regimens are scarce, leading to uncertainties in clinical decision-making.

In recent years, some researchers have conducted network meta-analyses on first-line chemotherapy drugs for pancreatic cancer [7–9]. These analyses compare the relative efficacy and safety of different chemotherapy regimens, providing crucial information for clinical decision-making. For instance, by analyzing various chemotherapy protocols in terms of overall survival, disease-free survival, and treatment-related toxicities, these analyses offer valuable insights for clinicians in selecting the most suitable treatment for patients. Nevertheless, it is important to acknowledge that these network meta-analyses are not without limitations and potential drawbacks. Firstly, the inclusion of non-randomized controlled trials in some analyses may introduce a degree of uncertainty and reduce the reliability of the evidence base. Secondly, the incorporation of studies that are not exclusively phase III clinical trials may introduce additional confounding factors that could impact the analysis.

This study aimed to perform a network meta-analysis (NMA) exclusively incorporating phase III randomized controlled trials to enhance the clinical reliability of the findings. By utilizing indirect comparisons between studies, this analysis evaluated the relative efficacy and safety of various chemotherapy regimens for advanced PDAC. This approach allows for the integration of results from multiple studies, offering a more comprehensive perspective on treatment options and valuable insights for optimizing patient care.

2. Materials and methods

2.1. Search strategy

We retrieved all articles published before 2022 in PubMed, Embase, and Cochrane Library databases. The combination of subject words and free words was adopted for retrieval with the following MeSH terms: "Pancreatic Neoplasms", "Drug Therapy", "Immunotherapy", "advanced", "unresectable", and "randomized". Limits included clinical trials.

2.2. Selection criteria

The literature met the following inclusion criteria: (1) published phase III randomized controlled trials (RCTs); (2) histologically confirmed advanced PDAC; (3) first-line chemotherapy for advanced PDAC patients; (4) primary outcome indicators of overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and adverse events (AEs), including grade $\geq$3 anemia, neutropenia, thrombocytopenia, and nausea. The exclusion criteria were: (1) non-English articles, letters, reviews, case reports, non-human studies, and articles without raw data; (2) non-randomized controlled single-arm studies; (3) studies comparing chemotherapy with adjuvant or neoadjuvant treatment; (4) studies including only patients with specific gene mutations.

2.3. Data extraction and quality assessment

Two researchers independently extracted data and recorded the following information in a Microsoft Excel spreadsheet: study number, first author, publication year, patient sex, age, sample size for each group, treatment plan, test and control group usage, OS, PFS, ORR, and occurrence of AEs, including grade $\geq$3 anemia, neutropenia, thrombocytopenia, and nausea. The quality of all included literature was evaluated by the two researchers using the RCT Cochrane Reviewer bias risk assessment criteria.

2.4. Statistical analysis

The primary endpoints of this NMA were OS, PFS, and ORR, while the secondary endpoint was AEs. OS was defined as the time from random assignment to death, while PFS was measured from randomization to documentation of disease progression or death. ORR was calculated as the proportion of complete and partial responses as defined in ERTCC v 3.0, divided by the total number of patients per arm. AEs of grade 3 and above were specified a priori, including anemia, neutropenia, thrombocytopenia, and nausea, as defined in the Common Terminology Criteria for Adverse Events (CTCAE) v 3.0 [10].

The NMA was conducted using STATA 17.0 (Stata Corporation, College Station, TX, USA). Hazard ratios (HRs) with 95 % confidence intervals (CIs) were used to measure PFS and OS, while odds ratios (ORs) with corresponding 95 % CIs were used for binary variables (ORR and AEs). Local and global inconsistency tests were used to check network consistency. Local inconsistencies between direct and indirect impact estimates were evaluated for each closed loop in the network. Due to heterogeneity among studies, a random-effects consistency model was used for all data analyses. The overall effect size was assessed using a Z test, with a *P*-value $<$00.05 considered statistically significant.

A network evidence plot was created, with interventions represented as nodes, node size indicating sample size, and line width proportional to the number of trials with related comparisons. The frequentist method was used to estimate the overall ranking of

treatments through NMA by calculating the ranking probability of each method. Stacked charts and surface under the cumulative ranking (SUCRA) curve were used to determine the efficacy and toxicity ranks of different chemotherapy regimens. A higher SUCRA value indicated a better or less toxic treatment option. Publication bias was evaluated using a "comparison-adjusted" funnel plot.

3. Results

3.1. Study selection and characteristics

We searched a total of 1645 records and removed 624 duplicates. After preliminary screening of 1021 papers based on title and abstract, we screened the full text based on inclusion and exclusion criteria, resulting in 24 studies meeting the criteria for further analysis. The flowchart of literature screening is shown in Fig. 1, and Table 1 summarizes the basic features of the included studies. All studies were published before 2021 and included 11,470 patients with advanced PDAC and 25 treatments. The evidence network of all enrolled studies is displayed in Fig. 2.

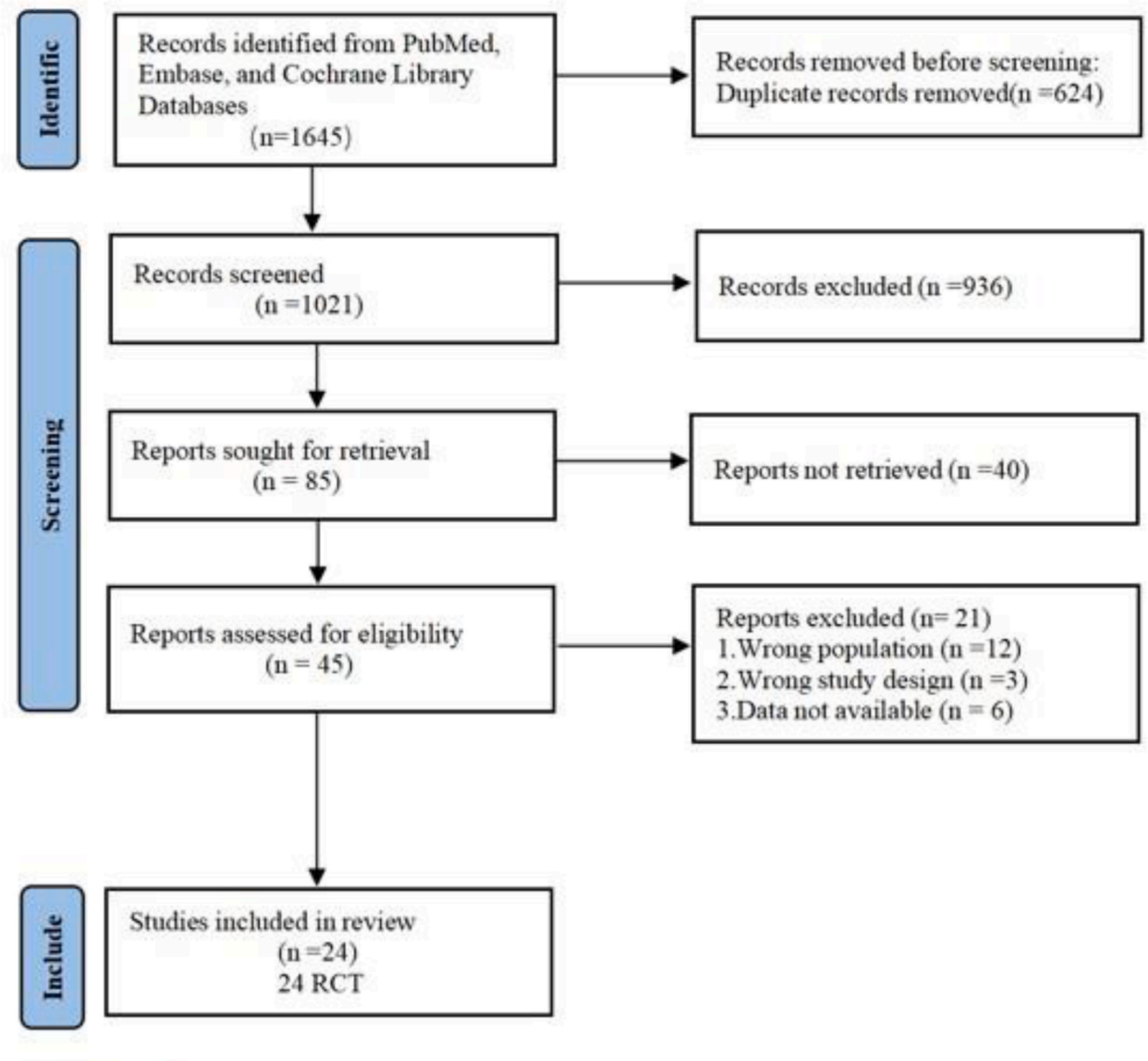

Fig. 1. Flow chart of randomized controlled clinical trials evaluating treatments for advanced pancreatic cancer through selection process.

Table 1
Characteristics of eligible randomized clinical trials included network meta-analysis.

Study:Author (year)	Study design: number of patients	Regimens:arm 1	Regimens: arm 2	Regimens:arm 3	Outcomes	Gender (M/F)	Median age (years)
Moore(2003) [17]	RCT- single blinded N1 = 139 N2 = 138	Gemcitabine (1000 mg/m^2)	BAY 12-9566	_	OS PFS	158/119	66
VanCustem (2004) [18]	RCT- double blinded N1 = 347 N2 = 341	Gemcitabine (1000 mg/m^2)	Gem + Tipifarnib	_	OS PFS ORR	395/293	62
Reni(2005) [14]	RCT-unblinded N1 = 47 N2 = 52	Gemcitabine (1000 mg/m^2)	PEFG	_	OS PFS	48/51	60
Louvet (2005) [19]	RCT- single blinded N1 = 156 N2 = 157	Gemcitabine (1000 mg/m^2)	Gem + Oxaliplatin	_	OS PFS ORR	177/136	61
Oettle (2005) [20]	RCT- single blinded N1 = 282 N2 = 283	Gemcitabine (1000 mg/m^2)	Gem + Pemetrexed	_	OS PFS ORR	322/243	63
Abou-Alfa (2006) [21]	RCT- single blinded N1 = 174 N2 = 175	Gemcitabine (1000 mg/m^2)	Gem + Exatecan	_	OS ORR	191/158	63
Heinemann (2006) [22]	RCT- single blinded N = 97 N2 = 98	Gemcitabine (1000 mg/m^2)	Gem + Cisplatin	_	OS PFS ORR	124/71	65
Stathopoulos (2006) [23]	RCT- single blinded N1 = 70 N2 = 60	Gemcitabine (1000 mg/m^2)	Gem + Irinotecan	_	OS ORR	81/49	64
Herrmann (2007) [24]	RCT- single blinded N1 = 159 N2 = 160	Gemcitabine (1000 mg/m^2)	Gem + Capecitabine	_	OS PFS ORR	171/148	_
Moore (2007) [25]	RCT- double blinded N1 = 284 N2 = 285	Gemcitabine (1000 mg/m^2)	Gem + Erlotinib	_	OS PFS ORR	298/271	64
Cunningham (2009) [26]	RCT- single blinded N1 = 266 N2 = 267	Gemcitabine (1000 mg/m^2)	Gem + Capecitabine	_	OS PFS ORR	313/220	62
Poplin (2009) [27]	RCT- single blinded N1 = 275 N2 = 277 N3 = 272	Gemcitabine (1000 mg/m131)	Gem + Oxaliplatin	GEM (FDR)	OS PFS ORR	439/385	63
VanCustem (2009) [28]	RCT- double blinded N1 = 306 N2 = 301	Gemcitabine + Erlotinib	Gem + Erlotinib + Bevacizumab	_	OS PFS ORR	362/245	62
Colucci (2010) [29]	RCT- single blinded N1 = 199 N2 = 201	Gemcitabine (1000 mg/m^2)	Gem + Cisplatin	_	OS PFS ORR	238/162	63
Philip (2010) [30]	RCT- single blinded N1 = 371 N2 = 372	Gemcitabine (1000 mg/m^2)	Gem + Cetuximab	_	OS PFS ORR	390/353	64
Kindler (2010) [31]	RCT- double blinded N1 = 300 N2 = 302	Gemcitabine (1000 mg/m^2)	Gem + bevacizumab	_	OS PFS ORR	328/274	64
Conroy (2011) [32]	RCT- single blinded N1 = 371 N2 = 372	Gemcitabine (1000 mg/m^2)	FOLFIRINOX	_	OS PFS ORR	211/131	61
Goncalves (2012) [33]	RCT- double blinded N1 = 52 N2 = 52	Gemcitabine (1000 mg/m^2)	Gem + Sorafenib	_	OS PFS ORR	62/42	63
Rougier (2013) [34]	RCT- double blinded N = 275 N2 = 271	Gemcitabine (1000 mg/m^2)	Gem + aflibercept	_	OS PFS	317/229	62
Goldstein (2015) [35]	RCT- single blinded N1 = 430 N2 = 431	Gemcitabine (1000 mg/m^2)	Gem + NPTX	_	OS PFS ORR	499/362	63
Fuchs (2015) [36]	RCT- double blinded N1 = 322 N2 = 318 N3 = 160	Gemcitabine (1000 mg/m^2)	Gem + Ganitumab 12 mg/kg	Gem + Ganitumab 20 mg/kg	OS PFS ORR	432/368	62
Deplanque (2015) [37]	RCT- double blinded N1 = 175 N2 = 173	Gemcitabine (1000 mg/m^2)	Gem + masitinib	_	OS	_	_
Okusaka (2017) [38]	RCT- single blinded N1 = 277 N2 = 280 N3 = 275	Gemcitabine (1000 mg/m^2)	Gem + S-1	S-1	OS PFS ORR	498/334	_
Temper (2021) [39]	RCT- double blinded N1 = 211 N2 = 213	Gem + Ibrutinib + NPTX	Gem + NPTX	_	OS PFS ORR	235/189	64

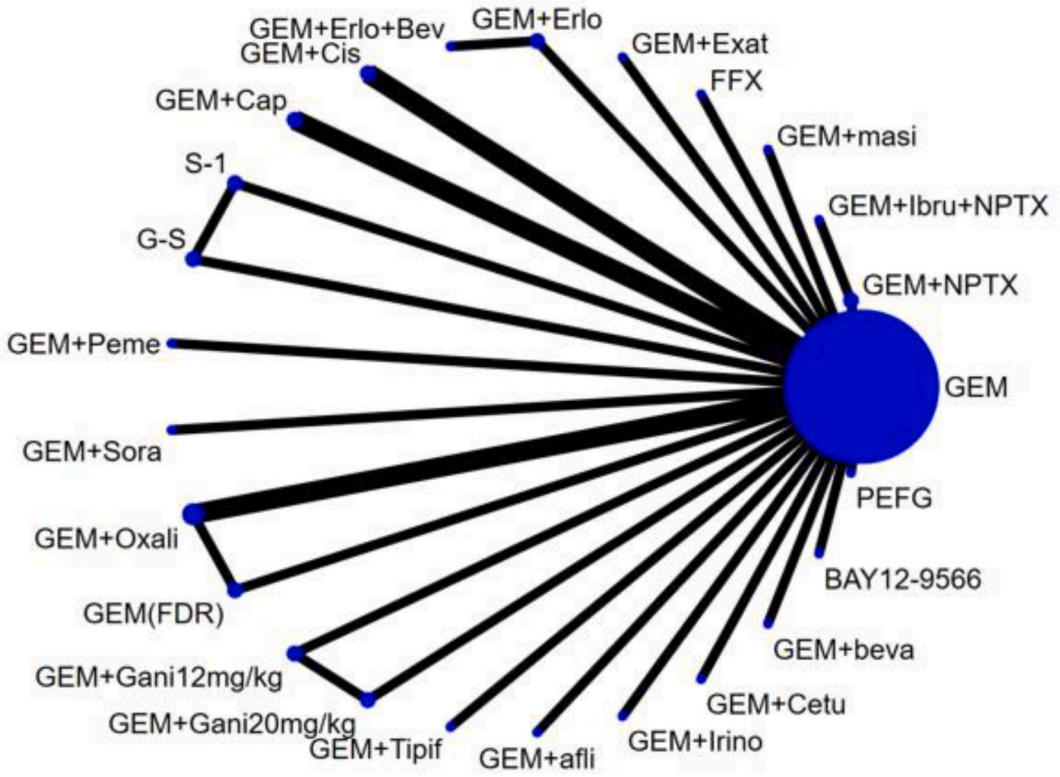

Fig. 2. Network evidence diagram of all the included studies. GEM: gemcitabine; NPTX: albumin-bound Paclitaxel; masi: masitinib; FFX: FOLFIRINOX; Exat: Exatecan; Cap: capecitabine; Cis: Cisplatin; G–S: gemcitabine + S-1; Peme: pemetrexed; Sora: sorafenib; Oxili: oxaliplatin; GEM (FDR): fixed-dose rate gemcitabine; Gani 12 mg/kg: Ganitumab 12 mg/kg; Gani 20 mg/kg: Ganitumab 20 mg/kg; Tipif: tipifarnib; afli: aflibercept; beva: bevacizumab; Irino: irinotecan; Cetu: cetuximab; Ibru: Ibrutinib; Erlo: erlotinib.

3.2. Network meta-analysis results for overall survival and progression-free survival

OS and PFS were reported in 14 and 11 studies, respectively, involving a total of 17 and 14 protocols. The network evidence diagrams are displayed in Fig. 3A and B, and the comparison of OS and PFS of each protocol obtained from NMA is shown in Table 2. The efficacy ranking of OS and PFS outcomes are shown in Fig. 4A and B, respectively, with FOLFIRINOX, GEM + NPTX, and G-S being the top 3 treatments for both outcomes. There was no inconsistency between direct and indirect comparisons, and all results were statistically significant ($p < 0.05$). The SUCRA diagram of each protocol is shown in Suppl. Figure 1, and the comparison-adjusted funnel plot for assessing publication bias is shown in Suppl. Figure 2.

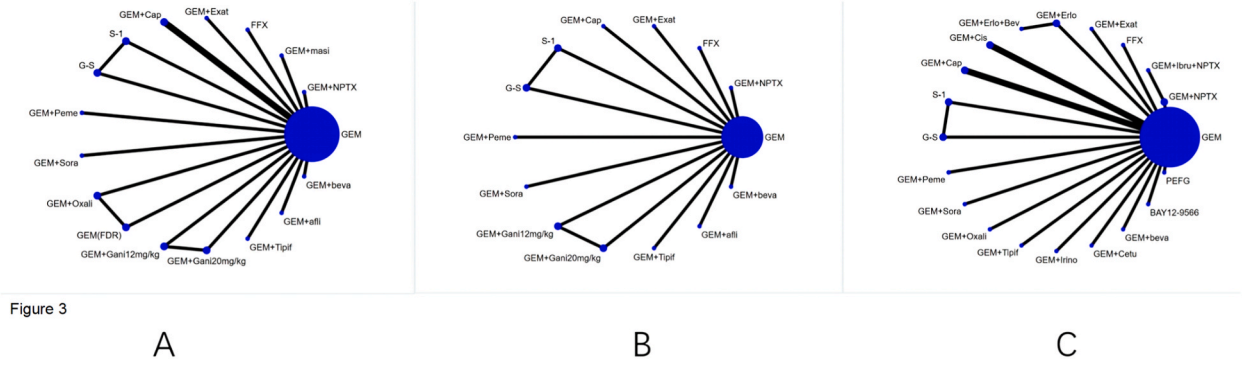

Fig. 3. (A) Network plot of OS; (B) Network plot of PFS; (C) Network plot of ORR. GEM: gemcitabine; NPTX: albumin-bound Paclitaxel; masi: masitinib; FFX: FOLFIRINOX; Exat: Exatecan; Cap: capecitabine; Cis: Cisplatin; G–S: gemcitabine + S-1; Peme: pemetrexed; Sora: sorafenib; Oxili: oxaliplatin; GEM(FDR): fixed-dose rate gemcitabine; Gani12 mg/kg: Ganitumab 12 mg/kg; Gani 20 mg/kg: Ganitumab 20 mg/kg; Tipif: tipifarnib; afli: aflibercept; beva: bevacizumab; Irino: irinotecan; Cetu: cetuximab; Ibru: Ibrutinib; Erlo: erlotinib.

Table 2
Log (HR) and 95 % confidence interval (95%CI) for OS and PFS from network meta-analysis.

Gem	2.18 (2.13,2.23)	-0.00 (-0.24,0.24)	4.50 (4.32,4.68)	0.25 (0.12,0.38)	0.65 (0.59,0.71)	0.35 (0.24,0.46)	1.25 (1.17,1.33)	-0.00 (-0.06,0.06)	-1.25 (-1.68,-0.82)	0.65 (0.59,0.71)	1.10 (1.04,1.16)	0.10 (0.02,0.18)	0.20 (0.10,0.30)	0.55 (0.49,0.61)	-0.95 (-1.04,-0.86)
	Gem + NPTX	-2.18 (-2.43,-1.93)	2.32 (2.14,2.50)	-1.93 (-2.07,-1.79)	-1.53 (-1.61,-1.45)	-1.83 (-1.95,-1.71)	-0.93 (-1.03,-0.83)	-2.18 (-2.26,-2.10)	-3.43 (-3.86,-3.00)	-1.53 (-1.61,-1.45)	-1.08 (-1.16,-1.00)	-2.08 (-2.18,-1.98)	-1.98 (-2.09,-1.87)	-1.63 (-1.71,-1.55)	-3.13 (-3.23,-3.03)
GEM+beva		Gem + masitinib	4.50 (4.20,4.80)	0.25 (-0.02,0.52)	0.65 (0.40,0.90)	0.35 (0.09,0.61)	1.25 (0.99,1.51)	-0.00 (-0.25,0.25)	-1.25 (-1.74,-0.76)	0.65 (0.40,0.90)	1.10 (0.85,1.35)	0.10 (-0.16,0.36)	0.20 (-0.06,0.46)	0.55 (0.30,0.80)	-0.95 (-1.21,-0.69)
0.70 (-1.65,3.05)	Gem+aflibercept		FFX	-4.25 (-4.47,-4.03)	-3.85 (-4.04,-3.66)	-4.15 (-4.36,-3.94)	-3.25 (-3.45,-3.05)	-4.50 (-4.69,-4.31)	-5.75 (-6.21,-5.29)	-3.85 (-4.04,-3.66)	-3.40 (-3.59,-3.21)	-4.40 (-4.60,-4.20)	-4.30 (-4.50,-4.10)	-3.95 (-4.14,-3.76)	-5.45 (-5.65,-5.25)
0.60 (-1.75,2.95)	-0.10 (-2.45,2.25)	Gem+Tipifarnib		Gem + Exatecan	0.40 (0.26,0.54)	0.10 (-0.07,0.27)	1.00 (0.85,1.15)	-0.25 (-0.39,-0.11)	-1.50 (-1.95,-1.05)	0.40 (0.26,0.54)	0.85 (0.71,0.99)	-0.15 (-0.30,0.00)	-0.05 (-0.21,0.11)	0.30 (0.16,0.44)	-1.20 (-1.35,-1.05)
0.55 (-1.80,2.90)	-0.15 (-2.50,2.20)	-0.05 (-2.40,2.30)	GEM+Ganni20 mg/kg		Gem+capecitabine	-0.30 (-0.43,-0.17)	0.60 (0.49,0.71)	-0.65 (-0.74,-0.56)	-1.90 (-2.33,-1.47)	-0.00 (-0.09,0.09)	0.45 (0.36,0.54)	-0.55 (-0.66,-0.44)	-0.45 (-0.57,-0.33)	-0.10 (-0.19,-0.01)	-1.60 (-1.71,-1.49)
1.05 (-1.30,3.40)	0.35 (-2.00,2.70)	0.45 (-1.90,2.80)	0.50 (-1.16,2.16)	GEM+Ganni12 mg/kg		S-1	0.90 (0.78,1.02)	-0.35 (-0.48,-0.22)	-1.60 (-2.04,-1.16)	0.30 (0.18,0.42)	0.75 (0.63,0.87)	-0.25 (-0.39,-0.11)	-0.15 (-0.30,-0.00)	0.20 (0.08,0.32)	-1.30 (-1.44,-1.16)
1.70 (-0.67,4.07)	1.00 (-1.37,3.37)	1.10 (-1.27,3.47)	1.15 (-1.22,3.52)	0.65 (-1.72,3.02)	Gem + Sorafenib		G-S	-1.25 (-1.35,-1.15)	-2.50 (-2.94,-2.06)	-0.60 (-0.70,-0.50)	-0.15 (-0.25,-0.05)	-1.15 (-1.27,-1.03)	-1.05 (-1.18,-0.92)	-0.70 (-0.80,-0.60)	-2.20 (-2.32,-2.08)
-0.30 (-2.65,2.05)	-1.00 (-3.35,1.35)	-0.90 (-3.25,1.45)	-0.85 (-3.20,1.50)	-1.35 (-3.70,1.00)	-2.00 (-4.37,0.37)	Gem+Pemetrexed		Gem+Pemetrexed	-1.25 (-1.68,-0.82)	0.65 (0.56,0.74)	1.10 (1.02,1.18)	0.10 (-0.00,0.20)	0.20 (0.08,0.32)	0.55 (0.46,0.64)	-0.95 (-1.06,-0.84)
-1.70 (-4.05,0.65)	-2.40 (-4.75,-0.05)	-2.30 (-4.65,0.05)	-2.25 (-4.60,0.10)	-2.75 (-5.10,-0.40)	-3.40 (-5.77,-1.03)	-1.40 (-3.75,0.95)	G-S		Gem + Sorafenib	1.90 (1.47,2.33)	2.35 (1.92,2.78)	1.35 (0.91,1.79)	1.45 (1.01,1.89)	1.80 (1.37,2.23)	0.30 (-0.14,0.74)
0.80 (-1.55,3.15)	0.10 (-2.25,2.45)	0.20 (-2.15,2.55)	0.25 (-2.10,2.60)	-0.25 (-2.60,2.10)	-0.90 (-3.27,1.47)	1.10 (-1.25,3.45)	2.50 (0.84,4.16)	S-1		Gem + Oxaliplatin	0.45 (0.38,0.52)	-0.55 (-0.65,-0.45)	-0.45 (-0.56,-0.34)	-0.10 (-0.18,-0.02)	-1.60 (-1.71,-1.49)
-0.00 (-2.04,2.04)	-0.70 (-2.74,1.34)	-0.60 (-2.64,1.43)	-0.55 (-2.59,1.49)	-1.05 (-3.09,0.98)	-1.70 (-3.76,0.36)	0.30 (-1.74,2.34)	1.70 (-0.34,3.74)	-0.80 (-2.84,1.24)	Gem+capecitabine		GEM(FDR)	-1.00 (-1.10,-0.90)	-0.90 (-1.01,-0.79)	-0.55 (-0.63,-0.47)	-2.05 (-2.15,-1.95)
0.60 (-1.75,2.95)	-0.10 (-2.45,2.25)	-0.00 (-2.35,2.35)	0.05 (-2.30,2.40)	-0.45 (-2.80,1.90)	-1.10 (-3.47,1.27)	0.90 (-1.45,3.25)	2.30 (-0.05,4.65)	-0.20 (-2.55,2.15)	0.60 (-1.44,2.64)	Gem + Exatecan		Gem+Gani12 mg/kg	0.10 (-0.01,0.21)	0.45 (0.35,0.55)	-1.05 (-1.17,-0.93)
-2.80 (-5.15,-0.45)	-3.50 (-5.85,-1.15)	-3.40 (-5.75,-1.05)	-3.35 (-5.70,-1.00)	-3.85 (-6.20,-1.50)	-4.50 (-6.87,-2.13)	-2.50 (-4.85,-0.15)	-1.10 (-3.45,1.25)	-3.60 (-5.95,-1.25)	-2.80 (-4.84,-0.76)	-3.40 (-5.75,-1.05)	FFX		Gem+Gani20 mg/kg	0.35 (0.23,0.47)	-1.15 (-1.28,-1.02)
-0.75 (-3.10,1.60)	-1.45 (-3.80,0.90)	-1.35 (-3.70,1.00)	-1.30 (-3.65,1.05)	-1.80 (-4.15,0.55)	-2.45 (-4.82,-0.08)	-0.45 (-2.80,1.90)	0.95 (-1.40,3.30)	-1.55 (-3.90,0.80)	-0.75 (-2.79,1.29)	-1.35 (-3.70,1.00)	2.05 (-0.30,4.40)	GEM+NPTX		Gem+Tipifarnib	-1.50 (-1.61,-1.39)
0.65 (-1.01,2.31)	-0.05 (-1.71,1.61)	0.05 (-1.61,1.71)	0.10 (-1.56,1.76)	-0.40 (-2.06,1.26)	-1.05 (-2.74,0.64)	0.95 (-0.71,2.61)	2.35 (0.69,4.01)	-0.15 (-1.81,1.51)	0.65 (-0.53,1.83)	0.05 (-1.61,1.71)	3.45 (1.79,5.11)	1.40 (-0.26,3.06)	GEM		Gem+aflibercept

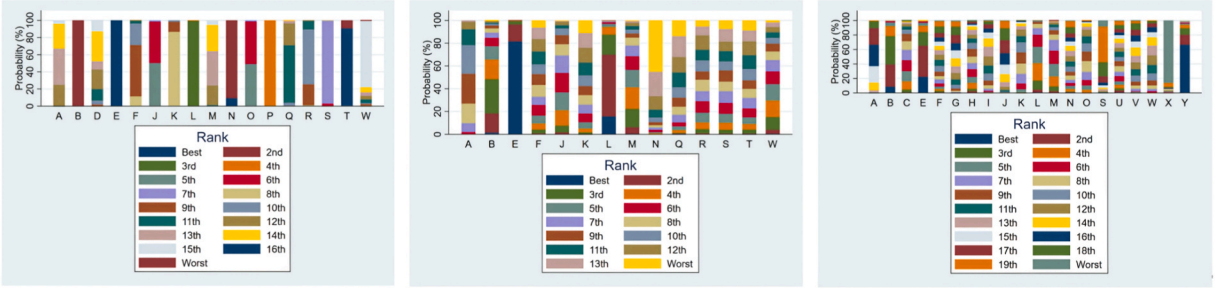

Figure 4

A B C

Fig. 4. Ranking in this network meta-analysis. (A): OS. (B): PFS. (C): ORR. Best represents the highest survival or remission rates. A: gemcitabine. B: gemcitabine + albumin-bound Paclitaxel; C: gemcitabine + Ibrutinib + albumin-bound Paclitaxel; D: gemcitabine + masitinib; E: FOLFIRINOX; F: gemcitabine + Exatecan; G: gemcitabine Erlotinib; H: gemcitabine + erlotinib + bevacizumab; I: gemcitabine + Cisplatin; J: gemcitabine + capecitabine; K: S-1; L: G-S; M: gemcitabine + pemetrexed; N: gemcitabine + sorafenib; O: gemcitabine + oxaliplatin; P: GEM(FDR); Q: gemcitabine + Ganitumab 12 mg/kg; R: gemcitabine + Ganitumab 20 mg/kg; S: gemcitabine + tipifarnib; T: gemcitabine + aflibercept; U: gemcitabine + irinotecan; V: gemcitabine + cetuximab; W: gemcitabine + bevacizumab; X: BAY 12–9566; Y: PEFG.

3.3. Network meta-analysis results for objective response rates

Among the included studies, 20 reported ORR for 20 treatment regimens, with the network evidence diagram shown in Fig. 3C. The efficacy comparison of each protocol obtained from NMA is shown in Table 3, with PEFG, FOLFIRINOX, and GEM + NPTX being the top 3 protocols with a statistically significant difference ($p < 0.05$) and SUCRA values of 95.4 %, 92.5 %, and 90.2 %, respectively. All studies showed no inconsistency or bias. The efficacy ranking is shown in Fig. 4C, and the SUCRA diagram of OS of each protocol is shown in Suppl. Figure 1. The comparison-adjusted funnel plot for assessing publication bias is shown in Suppl. Figure 2.

Table 3
The odds ratio and 95 % confidence interval (95%CI) of the ORR from network meta-analysis.

PEFG	0.03 (0.00,0.29)	0.20 (0.06,0.72)	0.19 (0.05,0.68)	0.24 (0.05,1.14)	0.11 (0.03,0.39)	0.26 (0.07,0.94)	0.20 (0.04,0.89)	0.35 (0.10,1.28)	0.40 (0.11,1.42)	0.26 (0.07,0.91)	0.15 (0.04,0.50)	0.20 (0.05,0.70)	0.27 (0.07,1.13)	0.16 (0.04,0.62)	0.20 (0.05,0.87)	0.67 (0.18,2.48)	0.32 (0.09,1.20)	0.57 (0.16,1.98)	0.15 (0.05,0.48)
	BAY 12-9566	7.98 (0.89,71.50)	7.34 (0.81,66.86)	9.35 (0.87,101.08)	4.18 (0.46,38.30)	10.28 (1.14,92.96)	7.81 (0.76,80.65)	13.81 (1.52,125.77)	15.97 (1.80,141.80)	10.21 (1.15,90.96)	5.78 (0.66,50.67)	7.72 (0.86,69.44)	10.80 (1.10,105.89)	6.50 (0.71,59.97)	7.95 (0.79,80.27)	26.33 (2.86,242.11)	12.86 (1.41,117.57)	22.61 (2.56,199.26)	5.89 (0.70,49.75)
		GEM+beva	0.92 (0.43,1.98)	1.17 (0.36,3.77)	0.52 (0.24,1.14)	1.29 (0.61,2.71)	0.98 (0.33,2.86)	1.73 (0.81,3.71)	2.00 (1.01,3.97)	1.28 (0.64,2.57)	0.72 (0.38,1.38)	0.97 (0.47,2.00)	1.35 (0.52,3.52)	0.82 (0.37,1.81)	1.00 (0.36,2.77)	3.30 (1.50,7.27)	1.61 (0.74,3.50)	2.83 (1.46,5.50)	0.74 (0.45,1.22)
			Gem+Cetuximab	1.27 (0.38,4.24)	0.57 (0.25,1.30)	1.40 (0.63,3.09)	1.06 (0.35,3.22)	1.88 (0.84,4.23)	2.18 (1.04,4.55)	1.39 (0.66,2.94)	0.79 (0.39,1.59)	1.05 (0.48,2.29)	1.47 (0.54,3.98)	0.89 (0.38,2.06)	1.08 (0.38,3.13)	3.59 (1.56,8.28)	1.75 (0.77,3.98)	3.08 (1.50,6.31)	0.80 (0.45,1.43)
				Gem+Irinotecan	0.45 (0.13,1.50)	1.10 (0.34,3.60)	0.84 (0.20,3.45)	1.48 (0.45,4.90)	1.71 (0.54,5.40)	1.09 (0.34,3.48)	0.62 (0.20,1.91)	0.83 (0.25,2.68)	1.15 (0.30,4.37)	0.70 (0.20,2.36)	0.85 (0.21,3.38)	2.82 (0.83,9.51)	1.37 (0.41,4.60)	2.42 (0.77,7.54)	0.63 (0.22,1.81)
					Gem+Tipifarnib	2.46 (1.10,5.51)	1.87 (0.61,5.72)	3.30 (1.45,7.53)	3.82 (1.80,8.12)	2.44 (1.14,5.25)	1.38 (0.67,2.83)	1.85 (0.84,4.07)	2.58 (0.94,7.07)	1.56 (0.66,3.67)	1.90 (0.65,5.55)	6.30 (2.69,14.73)	3.07 (1.33,7.09)	5.41 (2.60,11.25)	1.41 (0.78,2.55)
						Gem + Oxaliplatin	0.76 (0.25,2.27)	1.34 (0.61,2.96)	1.55 (0.76,3.18)	0.99 (0.48,2.05)	0.56 (0.29,1.11)	0.75 (0.35,1.60)	1.05 (0.40,2.79)	0.63 (0.28,1.44)	0.77 (0.27,2.20)	2.56 (1.13,5.79)	1.25 (0.56,2.79)	2.20 (1.10,4.40)	0.57 (0.33,0.99)
							Gem + Sorafenib	1.77 (0.59,5.34)	2.04 (0.71,5.87)	1.31 (0.45,3.78)	0.74 (0.26,2.07)	0.99 (0.34,2.91)	1.38 (0.40,4.81)	0.83 (0.27,2.58)	1.02 (0.28,3.73)	3.37 (1.09,10.38)	1.65 (0.54,5.02)	2.89 (1.02,8.18)	0.75 (0.29,1.94)
								Gem+Pemetrexed	1.16 (0.55,2.41)	0.74 (0.35,1.56)	0.42 (0.21,0.84)	0.56 (0.26,1.21)	0.78 (0.29,2.11)	0.47 (0.20,1.09)	0.58 (0.20,1.66)	1.91 (0.83,4.39)	0.93 (0.41,2.11)	1.64 (0.80,3.34)	0.43 (0.24,0.75)
									G-S	0.64 (0.42,0.97)	0.36 (0.20,0.67)	0.48 (0.24,0.97)	0.68 (0.27,1.72)	0.41 (0.19,0.88)	0.50 (0.18,1.36)	1.65 (0.77,3.54)	0.80 (0.38,1.70)	1.42 (0.75,2.66)	0.37 (0.23,0.59)
										S-1	0.57 (0.30,1.06)	0.76 (0.37,1.54)	1.06 (0.41,2.72)	0.64 (0.29,1.39)	0.78 (0.28,2.14)	2.58 (1.19,5.60)	1.26 (0.59,2.69)	2.21 (1.16,4.22)	0.58 (0.36,0.93)
											Gem+capecitabine	1.34 (0.69,2.58)	1.87 (0.75,4.63)	1.13 (0.54,2.35)	1.38 (0.52,3.66)	4.56 (2.20,9.44)	2.22 (1.09,4.54)	3.91 (2.17,7.04)	1.02 (0.68,1.52)
												Gem + Cisplatin	1.40 (0.53,3.67)	0.84 (0.38,1.89)	1.03 (0.37,2.89)	3.41 (1.53,7.60)	1.67 (0.76,3.66)	2.93 (1.49,5.76)	0.76 (0.45,1.29)
													GEM + Erlo + Bev	0.60 (0.36,1.02)	0.74 (0.22,2.46)	2.44 (0.88,6.72)	1.19 (0.44,3.24)	2.09 (0.84,5.25)	0.55 (0.24,1.23)
														Gem + Erlotinib	1.22 (0.41,3.61)	4.05 (1.70,9.63)	1.98 (0.84,4.64)	3.48 (1.64,7.37)	0.91 (0.49,1.68)
															Gem + Exatecan	3.31 (1.13,9.74)	1.62 (0.56,4.70)	2.84 (1.06,7.64)	0.74 (0.30,1.81)
																FFX	0.49 (0.21,1.14)	0.86 (0.41,1.81)	0.22 (0.12,0.41)
																	GEM + Ibru + NPTX	1.76 (1.18,2.63)	0.46 (0.25,0.82)
																		GEM+NPTX	0.26 (0.17,0.40)
																			GEM

3.4. Network meta-analysis results for adverse events

The network evidence diagrams for AE analysis based on all included studies are shown in Suppl. Figure 3. The top 3 protocols for anemia grade≥3 were GEM + sorafenib, GEM + oxaliplatin, and GEM + Ganitumab 20 mg/kg (SUCRA: 99.1 %, 93 %, and 80.5 %, respectively); for neutropenia, S-1, GEM + oxaliplatin, and GEM + Ganitumab 20 mg/kg (SUCRA: 81.7 %, 82.5 %, and 74.5 %, respectively); for thrombocytopenia, S-1, GEM + sorafenib, and GEM + cetuximab (SUCRA: 84.1 %, 66.5 %, 60.9 %, respectively); and for nausea, Ganitumab 20 mg/kg GEM, GEM + Ganitumab 12 mg/kg, and GEM + tipifarnib (SUCRA: 84.3 %, 80.4 %, and 72.4 %, respectively). A stacked chart of AEs for each protocol is shown in Suppl. Figure 4. All included studies showed no inconsistency, heterogeneity, or bias. The SUCRA diagram of OS of each protocol is shown in Suppl. Figure 5. A comparison of the four AEs after the use of each protocol obtained from NMA is shown in Suppl. Tables 1 and 2. The comparison-adjusted funnel plot for assessing publication bias is shown in Suppl. Figure 6.

4. Discussion

When dealing with advanced chemotherapy regimens for PDAC, data from direct comparisons are often limited, which hinders our understanding of the relative efficacy and safety of various regimens. In this context, NMA becomes particularly important.

The basic principle of NMA is that by comparing two or more treatments that share a common comparator (e.g., a control group), we can indirectly derive comparisons between these treatments. The advantage of this method is that it can provide a comprehensive assessment of all available treatments, not just those that have been directly compared [11].

Our NMA identified three chemotherapy regimens that may improve survival compared to GEM monotherapy and other regimens, with FOLFIRINOX ranking the highest. FOLFIRINOX includes four drugs: fluorouracil, leucovorin, irinotecan, and oxaliplatin. Fluorouracil inhibits tumor growth by blocking the synthesis of DNA and RNA, while leucovorin acts as a potentiator, enhancing the antitumor effect of fluorouracil. Irinotecan is a topoisomerase I inhibitor that prevents DNA unwinding, leading to DNA strand breaks and thus inhibiting DNA replication and transcription. Oxaliplatin forms adducts with DNA and platinum, causing DNA damage and preventing DNA replication and transcription [12]. The combined application of these four drugs enhances the cytotoxic effect on tumor cells, thereby effectively treating pancreatic cancer. However, it is important to note that FOLFIRINOX may lead to more adverse events than GEM alone, which could limit its clinical application.

GEM + NPTX, a combination of GEM and a solvent-free albumin-bound form of paclitaxel. The combination of GEM and NPTX has shown higher activity and stronger cytotoxicity than GEM alone, resulting in better survival advantage and higher median OS and PFS for patients with pancreatic cancer. The mechanistic basis for this improved survival is thought to be due to the enhanced transport of paclitaxel across the endothelial cells and greater delivery of paclitaxel to tumors inhibits cell division by preventing microtubule depolymerization, but further research is needed to confirm this [13].

PEFG obtained the highest rank and showed improved ORR compared to other regimens. In a study conducted by Reni et al., in 2005 [14], the ORR of PEFG was 38.5 %, which was significantly higher than the ORR of GEM which was only 8.5 %. Furthermore, the study also concluded that PEFG performed better than GEM in terms of OS and PFS. The common feature of the four drugs in the PEFG regimen is that they all interfere with the synthesis, replication, and transcription of DNA through different mechanisms, thereby inhibiting the growth and division of tumor cells. The combined application of these drugs enhances the cytotoxic effect on tumor cells, thereby effectively treating pancreatic cancer. This suggests that PEFG may be a more effective treatment option for patients with cancer compared to GEM. Nonetheless, it is crucial to acknowledge that despite the extended duration of the study, the small sample size may have amplified the influence of individual variability on the experimental outcomes. Consequently, future investigations employing this regimen should be conducted within a more substantial population cohort to mitigate these effects.

This investigation revealed that, in comparison to other treatment regimens, the integration of gemcitabine with targeted therapeutics led to a decrease in adverse events, with gemcitabine exhibiting diminished hematological toxicity. Sorafenib, an orally administered anticancer agent, specifically targets Ras-dependent signal transduction and angiogenesis pathways [12]. A Phase I clinical trial demonstrated that the gemcitabine-sorafenib combination exhibits commendable tolerability and efficacy in the management of advanced pancreatic ductal adenocarcinoma (PDAC) [15]. In a head-to-head comparison, the incidence of Grade 3 anemia was significantly lower with the gemcitabine-sorafenib regimen than with gemcitabine monotherapy (2 % vs 15 %) [16].

This research offers several advantages over previous studies. Firstly, we focused solely on phase III clinical RCTs, which enhances the clinical relevance of our analysis. Secondly, we evaluated all available first-line chemotherapy regimens for advanced PDAC based on high-quality RCTs. Finally, our study assessed the chemotherapy regimens with respect to a range of important outcomes, providing new insights into the benefit–risk ratios of various treatments.

This study has limitations. NMA, being an indirect comparison method, is subject to factors such as trial heterogeneity, bias, and inconsistency, which could affect the reported estimates. Additionally, not all the results of interest were consistently reported in all trials, meaning that for specific results, only a subset of the included literature could be analyzed by NMA. Finally, due to the large number of direct and indirect comparisons involved, we were unable to construct a contribution matrix or test local inconsistency.

In conclusion, this investigation utilized NMA to furnish robust data pertaining to the efficacy and safety of diverse therapeutic interventions for advanced PDAC, circumventing the need for direct comparative studies. The findings suggest that specific combination therapies may confer superior survival benefits, albeit potentially accompanied by heightened toxicity. When instituting chemotherapy regimens in a clinical milieu, a holistic assessment of the patient's overall health status and drug tolerance is indispensable. To further refine our understanding of the relative efficacy and safety of various chemotherapy regimens, the execution of additional rigorous clinical trials and high-caliber NMA analyses is necessitated.

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Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Mao-Ji Kang: Writing – original draft, Data curation, Formal analysis, Software. **Hao-Xin Li:** Formal analysis, Software, Writing – original draft, Writing – review & editing. **Yu Gan:** Conceptualization, Writing – review & editing. **Cheng Fang:** Conceptualization, Writing – review & editing. **Xiao-Li Yang:** Conceptualization, Writing – review & editing. **Bo Li:** Conceptualization, Supervision, Writing – review & editing. **Song Su:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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