Meta-analysis of current chemotherapy regimens in advanced pancreatic cancer to prolong survival and reduce treatment-associated toxicities

JIE CHEN[1,2*], LINLI CHEN[3*], JIANPING YU[4*], YANMEI XU[3*], XIAOHUI WANG[5], ZIQIAN ZENG[6], NING LIU[7], FAN XU[6,8] and SHU YANG[6]

[1]School of Chinese Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, SAR 999077; [2]Department of Orthopedics, Shanghai Institute of Traumatology and Orthopaedics, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200025; [3]Division of General Practice, West China Hospital, Sichuan University, Chengdu, Sichuan 610041; [4]Department of Neurology, The First Affiliated Hospital of Chengdu Medical College, Chengdu, Sichuan 610500; [5]Department of General Surgery, Bayingol Mongolia Autonomous Prefecture People's Hospital, Urumqi, Xinjiang Uygur Autonomous Region 841300; [6]Public Health School, Chengdu Medical College, Chengdu, Sichuan 610500; [7]Department of Medicine, Sunshine Guojian Pharmaceutical Co., Ltd., Shanghai 201203; [8]Interdisciplinary Division of Biomedical Engineering, The Hong Kong Polytechnic University, Hong Kong, SAR 999077, P.R. China

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Abstract. Unresectable advanced pancreatic cancer (APC) is a highly lethal malignancy. Although numerous chemotherapeutic regimens are available, evidence regarding the survival extension, the life quality improvement, the associated risks and occurrence rates of adverse effects, is required. The effects of 19 chemotherapy regimens on survival and treatment-associated toxicities in the context of APC treatment were comparatively assessed. A total of 23 randomized controlled trials were included in this network meta-analysis. For overall survival, five regimens, Gemcitabine (Gem)+radiotherapy (Radio), Gem+cisplatin (Cis), Gem+erlotinib (Erl)+bevacizumab (Bev), Gem+capecitabine (Cap)+Erl, and Gem+exatecan, were the most effective treatments, according to their respective high surface under the cumulative ranking (SUCRA) probabilities. Regarding the progression-free survival, five regimens, including Gem+Radio, Gem+Erl+Bev, Gem+Cis, Gem+Cap+Erl and Gem+pemetrexed, were the most effective treatments based on their SUCRA probabilities. Each regimen exhibited advantages and disadvantages, and 14 common treatment-associated toxicities were present in different proportions. The three principal toxic effects included haematological, gastrointestinal and constitutional symptoms. To improve survival, chemotherapy regimens with high SUCRA probabilities require prioritizing. Although treatment-associated toxicities are unavoidable, the regimens presented toxicities in distinct proportions. Therefore, clinicians should assess the disease status of the patients, and balance the benefits and risks of the selected treatment.

Correspondence to: Professor Fan Xu, Interdisciplinary Division of Biomedical Engineering, The Hong Kong Polytechnic University, Block S104, 11 Yuk Choi Road, Hung Hom, Kowloon, Hong Kong, SAR 999077, P.R. China
E-mail: xufan@cmc.edu.cn

Dr Shu Yang, Public Health School, Chengdu Medical College, 783 Xindu Avenue, Chengdu, Sichuan 610500, P.R. China
E-mail: shuyangcmc@163.com

*Contributed equally

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Introduction

Unresectable advanced pancreatic cancer (APC) is the most lethal and the most aggressive human cancer (1). APC is predicted to increase from the 4th to the 2nd leading cause of mortality in the USA by 2020 due to its lethal and malignant characteristics (2). Due to the limitations of diagnostic techniques, the majority of patients and clinicians become aware of the disease too late, as this cancer is frequently diagnosed in an advanced stage (3,4). APC is characterized by a high mortality rate worldwide, 90.8% in China (5), 78.5% in the USA (6) and 95.0% in Canada (7).

Gemcitabine (Gem) was more effective compared with 5-fluorouracil (5-FU) in patients with APC and improved the survival rate; therefore, it was approved as a first-line regimen by the US Food and Drug Administration (FDA) in 1996 (8). At present, the majority of chemotherapy regimens are derived from Gem, which was used as the control treatment in numerous previous studies (9-11).

Although a number of combination chemotherapy regimens containing Gem (Gem+Xs) or monotherapies have become more prevalent over the past decades (12), the improvement of the conditions of the patients has been limited (12-15). For example, the poor prognosis of APC leads to a low survival rate (14,16,17), which has remained relatively unaltered for ~5 decades (15). Nevertheless, the benefits and risks of combination chemotherapy regimens remain unclear. Therefore, first-line chemotherapy regimen data were pooled to comprehensively evaluate the benefits and risks of these treatments.

Materials and methods

Study design. In order to assess the benefits and risks of various chemotherapy regimens in distinct conditions, head-to-head comparison clinical trials were selected. This network meta-analysis followed the preferred reporting items of system reviews and meta-analysis (PRISMA) statement (18) while integrating evidence from direct and indirect treatment comparisons (19). The flow chart for study selection is presented in Fig. 1.

Search strategy. The comprehensive search strategy was conducted using the MEDLINE (www.pubmed.com), EMBASE (www.embase.com), Cochrane Central Register of Controlled Trails (www.cochranelibrary.com) and ClinicalTrials.gov (https://ClinicalTrials.gov) databases with the following search terms: (Advanced pancreatic cancer or pancreatic cancer) AND (advanced pancreatic cancer or chemotherapy regimens). The drug abbreviations and the combinations tested are listed in Table I.

Table I. Abbreviation list of chemistry regimens.

Abbreviation	Chemistry regimens
Gem	Gemcitabine
Gem+Axit	Gemcitabine+axitinib
Gem+5-FU	Gemcitabine+5-fluorouracil
Gem+Cap+Erl	Gemcitabine+capecitabin+erlotinib
Gem+Cap	Gemcitabine+capecitabine
Gem+Cet	Gemcitabine+cetuximab
Gem+Cis	Gemcitabine+cisplatin
Gem+Erl	Gemcitabine+erlotinib
Gem+Erl+Bev	Gemcitabine+erlotinib+bevacizumab
Gem+Eta	Gemcitabine+etanercept
Gem+Exa	Gemcitabine+exatecan
Gem+Iri	Gemcitabine+irinotecan
Gem+Mar	Gemcitabine+marismastat
Gem+Nab-p	Gemcitabine+nab-paclitaxel
Gem+Pem	Gemcitabine+pemetrexed
Gem+Radio	Gemcitabine+radiotherapy
Gem+Sor	Gemcitabine+sorafenib
Gem+Tip	Gemcitabine+tipifarnib
Gem+Vis	Gemcitabine+vismodegib
Oxa+Iri+Leu+Flu+Inf	Oxaliplatin+irinotecan+ leucovorin+fluorouracil+infusion

Study selection criteria and outcomes. Experienced investigators independently selected the studies and extracted the data, and any conflicts were resolved in discussion. The study selection criteria were based on the National Comprehensive Cancer Network 2017 criteria (20). The following inclusion criteria were applied: (i) Parallel-group randomized controlled trials (RCTs; phase II or III) with the Gem intervention set as the common comparison treatment and including ≥2 arms; (ii) a minimum 6-month follow-up period; (iii) patients ≥18 years old (i.e., adult patients); (iv) diagnosis of unresectable APC; (v) application of palliative treatments, including invasive radiation therapy, chemotherapy or chemoradiation therapy, targeted therapies or combination therapy with the respective placebo or control group; (vi) either fixed-dose or flexible-dose RCTs with dose titration; and (vii) the patient performance status reported as 0-2 scores in the Eastern cooperative oncology group or 70-80% in Karnofsky scales (21). Previous studies that (i) included patients undergoing radical resection, (ii) failed to report the number of patients, (iii) failed to report the primary efficacy outcome [progression-free survival (PFS)], or (iv) failed to report the data necessary to estimate the standard deviation of the primary efficacy outcome were excluded.

Data extraction. The following data were extracted from each included RCT: First author's name, published year, clinical phase, sample size of each arm, age, treatment, dosage, route, duration, overall survival (OS) in months, PFS in months, and 14 treatment-associated categories of side effects associated with quality of life ('hepatotoxicity', 'haematological', 'mental/psychiatry', 'renal toxicity', 'gastrointestinal', 'neuropathy', 'electrolytes imbalance', 'pain', 'infection', 'skin', 'constitutional symptoms', 'cardiac/vascular', 'pulmonary' and 'other'). The details of the outcomes of the included studies are presented in Table II.

Risk of bias assessment. To reduce the risk bias, the recommended approach of Cochrane reviews was followed and the risk was assessed throughout the process (22). The following bias sources were independently assessed: Random sequence generation, allocation concealment, blinding of investigators and/or patients, blinding of outcome assessment and the degree of data incompleteness. Each bias was scored as low, unclear or high, as presented in Table III.

Statistical analysis. All statistical analyses were performed using the network meta-analysis package in Stata (version 13.0; StataCorp LP, College Station, TX, USA) (19). For the endpoint outcomes, OS and PFS data were extracted from references as medians and subsequently transformed into standardized mean differences with 95% confidence intervals (CIs). A network meta-analysis was conducted following the standard workflow (19). The network map presents the connection status of the studies; no loops and a P-value >0.05 validated the consistency model to perform the network meta-analysis. Heterogeneity was assessed with the I^2 metric. Heterogeneity was 0% for OS and 75.64% for PFS. Therefore, the Mantel-Haenszel fixed-effects model was used for OS, and the Mantel-Haenszel random-effects model was used for PFS (21). All of the studies with various

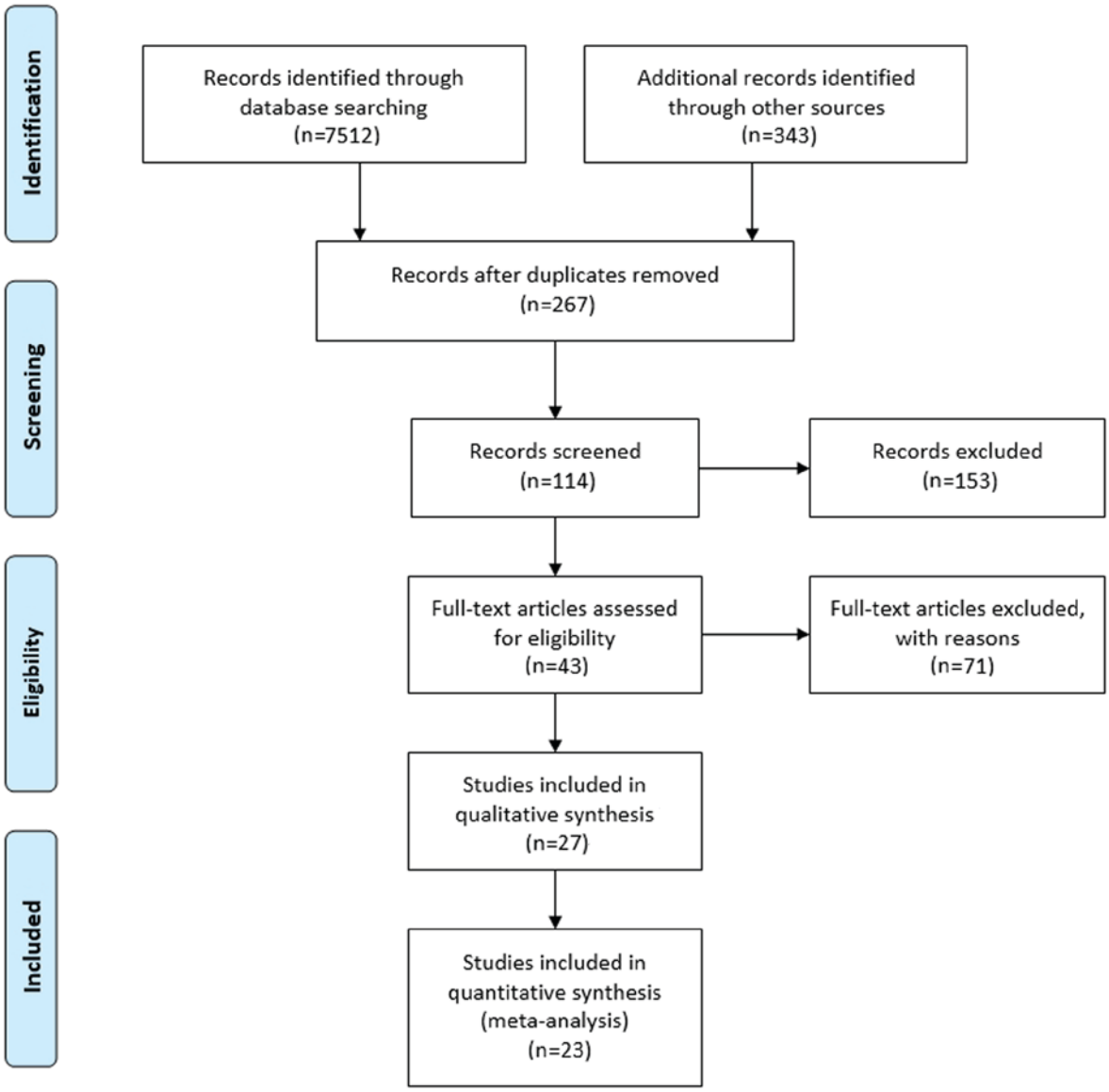

Figure 1. Flow chart of study selection.

treatments were included as drugs that were either directly or indirectly associated with a common comparator (Gem only) for further downstream ranking analysis. Subsequently, to rank the effects of the treatments, the analysis of the surface under the cumulative ranking (SUCRA) probabilities was performed under the protocol of Stata (19), and the results are presented as the percentage of the efficacy of each intervention relative to a hypothetical ideal intervention (23). A larger SUCRA score indicated longer OS and PFS.

The data are presented in an ordinal data format according to the 14 categories of side effects. Network meta-analyses were separately conducted, and the data were calculated as hazard ratios with 95% CIs. To examine and classify the adverse effects that occurred among the different treatments, a stack bar graph of each category was generated.

Results

Standard workflow via PRISMA. To ensure the general quality of the present study, a PRISMA flowchart regarding the screening process of the study used, is presented in Fig. 1. From an initial set of 7,855 non-duplicated studies, a total of 23 RCTs were included in this analysis. The drug abbreviations and the combinations assessed are listed in Table I, and the general characteristics of the included RCTs or studies are presented in Table II. The risk of bias assessment for these included RCTs is depicted in Table III. The geometry evidence of the OS network plot and its associated pooled forest plot are summarized in Fig. 2. Furthermore, the geometry evidence of the PFS network plot and its associated pooled forest plot are summarized in Fig. 3. Using SUCRA, graphs of the rank of the treatments associated with OS and PFS are listed in Fig. 4, and the 14 types of treatment-associated toxicities are presented in Fig. 5.

Network diagram (geometry and forest). Numerous combinations of various treatments were analyzed. The network maps of OS and PFS demonstrated the geometry of 18 chemotherapy regimens compared with a common treatment, Gem, and no loops were identified (Figs. 2A and 3A). Furthermore, the network

Table II. General characteristics of the included studies.

Author, year	Phase	N	Median age, years (range)	Regimens	Dose	Route	Duration, median (range) or mean ± SD	Overall survival, months mean (95% CI)	Progression-free survival, months mean (95% CI)	(Refs.)
Cunningham *et al*, 2009	3	266	62 (26-83)	Gem	Gem (1,000 mg/m^2/week) weekly	IV		6.2	3.8	(30)
	3	267	62 (37-82)	Gem+Cap	Gem (1,000 mg/m^2/week) + Cap 1,660 mg/m^2/day	IV and oral		7.1	5.3	
Conroy *et al*, 2005	N/A	171	61 (34-75)	Gem	Gem (1,000 mg/m^2/week)	IV	10 weeks	6.8 (5.5-7.6)	3.3 (2.2-3.6)	(32)
	N/A	171	61 (25-76)	Oxa+Iri+ Leu+Flu	Oxi (85 mg/m^2) + Iri (180 mg/m^2 + Leu (400 mg/m^2) + Flu (400 mg/m^2)	IV	10 weeks	11.1 (9.0-13.1)	6.4 (5.5-7.2)	
Berlin *et al*, 2002	3	162	64.3	Gem	Gem (1,000 mg/m^2/week)	IV	3 weeks of every 4	5.4	2.2	(41)
	3	160	65.8	Gem+5-FU	Gem (1,000 mg/m^2/week) + 5-FU (600 mg/m^2/week)	IV and bolus	3 weeks of every 4	6.7	3.4	
Bramhall *et al*, 2002	N/A	119	62 (37-85)	Gem	Gem (1,000 mg/m^2/week)	IV	10 weeks	5.47	3.2	(42)
	N/A	120	62 (32-83)	Gem+Mar	Gem (1,000 mg/m^2/week) + Mar 10 mg b.i.d.	IV and bolus	10 weeks	5.52	3.08	
Rocha Lima *et al*, 2004	3	180	60.2 (32.3-82.9)	Gem	Gem (1,000 mg/m^2/week)	IV	12.9 weeks (6.6-88)	6.6 (0.03-22.8)	3.0 (2.5-3.7)	(43)
	3	180	63.2 (38.7-81.2)	Gem+Iri	Gem (1,000 mg/m^2/week) + Iri 100 mg/m^2	IV	12.1 weeks (3.0-83.9)	6.3 (0.2-23.8)	3.5 (2.8-4.2)	
Van Cutsem *et al*, 2004	3	347	62 (30-88)	Gem	Gem (1,000 mg/m^2/week)	IV	14 weeks	6.07	3.63	(44)
	3	341	61 (29-89)	Gem+Tip	Gem (1,000 mg/m^2/week) + Tip 200 mg b.i.d.	IV and bolus	12.1 weeks	6.43	3.73	
Oettle *et al*, 2005	3	273	63 (28-82)	Gem	Gem (1,250 mg/m^2/week)	IV	12 weeks	6.2 (5.4-6.9)	3.3 (2.5-3.6)	(45)
	3	273	63 (27-83)	Gem+Pem	Gem (1,000 mg/m^2/week) + Pem 500 mg/m^2	IV	12 weeks	6.3 (5.4-6.9)	3.9 (3.3-4.7)	
Von Hoff *et al*, 2005	3	430	63	Gem	Gem (1,000 mg/m^2/week)	IV	3 months	6.7	3.7	(46)
	3	431	63	Gem+Nab-p	N/A	IV	4 months	8.5	5.5	
Abou-Alfa *et al*, 2006	3	174	62.3 (30-84)	Gem	Gem (1,000 mg/m^2/week)	IV	5.8±3.7	6.2 (5.2-7.5)	3.8 (3-4.3)	(47)

Table II. Continued.

Author, year	Phase	N	Median age, years (range)	Regimens	Dose	Route	Duration, median (range) or mean ± SD	Overall survival, months mean (95% CI)	Progression-free survival, months mean (95% CI)	(Refs.)
	3	175	63 (36-85)	Gem+Exa	Gem (1,000 mg/m^2/week) + Exa 2.0 mg/m^2	IV	months 6.4±4.2 months	6.7 (5.4-7.9)	3.7 (2.7-4.7)	
Heinemann *et al*, 2006	3	97	66 (43-85)	Gem	Gem (1,000 mg/m^2/week)	IV	4.1 months	7.5	5.3	(48)
	3	98	64 (37-82)	Gem+Cis	Gem (1,000 mg/m^2/week) + Cis 50 mg/m^2	IV	3.3 months	6	3.1	
Stathopoulos *et al*, 2006	3	70	64 (44-83)	Gem	Gem (900 mg/m^2/week)	IV	12 weeks	6.5	2.9	(49)
	3	60	64 (31-84)	Gem+Irl	Gem (900 mg/m^2/week) + Iri 300 mg/m^2	IV	9 weeks	6.4	2.8	
Herrmann *et al*, 2007	3	159	N/A	Gem	Gem (1,000 mg/m^2/week)	IV		7.2	3.9	(50)
	3	159	N/A	Gem+Cap	Gem (1,000 mg/m^2/week) + Cap 650 mg/m^2	IV and oral		8.4	4.3	
Moore *et al*, 2007	3	284	64.0 (36.1-92.4)	Gem	Gem (1,000 mg/m^2/week)	IV		5.91	3.55	(51)
	3	285	63.7 (37.9-84.4)	Gem+Erl	Gem (1,000 mg/m^2/week) + Erl 100 mg/days	IV		6.24	3.75	
Spano *et al*, 2008	2	34	61 (36-78)	Gem	Gem 1,000 mg/m^2 on days 1,8 and 15 in 4-week cycles	IV	4 (1-12) cycles	5.6 (3.9-8.8)	3.7 (2.2-6.7)	(52)
	2	69	65 (44-81)	Gem+Axi	Gem 1,000 mg/m^2 on day Axi 5 mg b.i.d.	PO	Axitinib 113 (7-481) days, Gemcitabine 5 (1-18) cycles	6.9 (5.3-10.1)	4.2 (3.6-10.2)	
Colucci *et al*, 2010	3	199	63 (37-75)	Gem	Gem (1,000 mg/m^2/week)	IV	8 cycles	8.3	3.9	(40)
	3	201	63 (35-75)	Gem+Cis	Gem (1,000 mg/m^2/week) + Cis 25 mg/m^2	IV	7 cycles	7.2	3.8	
Philip *et al*, 2010	3	371	64.3	Gem	Gem (1,000 mg/m^2/week)	IV		5.9	3	(53)
	3	372	63.7	Gem+Cet	Gem (1,000 mg/m^2/week) + Cet 400 mg/m^2	IV		6.3	3.4	
Kindler *et al*, 2011	3	316	62 (35-89)	Gem	Gem (1,000 mg/m^2/week) weekly	IV	2.3 (0.03-11.0) months	8.3 (6.9-10.3)	4.4 (3.7-5.2)	(54)

Table II. Continued.

Author, year	Phase	N	Median age, years (range)	Regimens	Dose	Route	Duration, median (range) or mean ± SD	Overall survival, months mean (95% CI)	Progression-free survival, months mean (95% CI)	(Refs.)
	3	314	61 (34-84)	Gem+Axi	Gem (1,000 mg/m^2/week) + Axi 10 mg/day	IV and oral	2.8 (0.03-11.0) months	8.5 (6.9-9.5)	4.4 (4.0-5.6)	
Loehrer *et al*, 2011	N/A	37	67±8.7[a] 69 (49.7-83.7)	Gem	1,000 mg/m^2/week for weeks 1 to 6, followed by 1 week rest. Following rest, for 3 of 4 weeks	IV	5.5 (2-8.3) weeks	9.2 (7.9-11.4)	6.7	(55)
	N/A	34	65.34±10.3[a] 66 (46.9-83.5)	Gem+Radio	600 mg/m^2/week	IV	5.5 (2-8.3) weeks	11.1 (7.6-15.5)	6	
Heinemann *et al*, 2012	N/A	143	65 (32-78)	Gem	Gem (1,000 mg/m^2/week)	IV	5 cycles (0-26)	6.9	3.2	(56)
	N/A	141	63 (38-75)	Gem+Cap+ Erl	Gem (1,000 mg/m^2/week) + Cap (1,000 mg/m^2 twice daily) + Erl (150 mg daily)	IV	5 cycles (0-26)	6.2	2.2	
Wu *et al*, 2013	1/2	8	59 (46-75)	Gem	Gem 1,000 mg/m^2 weekly for 7 weeks with a one-week rest, followed 1,000 mg/m^2 weekly for 3 weeks' with a one-week rest	IV	12.8 (8-22) weeks	8.1 (3.1-20.4)	4.3 (2.2-8.1)	(57)
	1/2	30	59 (46-81)	Gem+Eta	Eta 25 mg twice weekly	Subcutaneous	12.2 (2-40) weeks	5.43 (1.5-16.9)	2.23 (1.8-7.4)	
Moehler *et al*, 2014	2	48	64.5 (36-84)	Gem	Gem (1,000 mg/m^2) was administered on days 1, 8, 15, 22, 29, 36 and 43 of the first cycle (8 weeks duration) and days 1, 8 and 15 of all subsequent cycles (4 weeks duration)	IV	4.2 (0.3-21.4) months	4.9 (3.5-7.7)	4.9 (3.5-7.7)	(58)
	2	49	64.0 (44-83)	Gem+Sor	Sor 400 mg	IV and PO	2.3 (0-19.1) months	3 (1.8-7.2)	3 (1.8-7.2)	
Catenacci *et al*, 2015	1b/2	53	64 (39-84)	Gem	Gem 1,000 mg/m2 IV over 30 min on days 1, 8 and 15 every 28 days	IV	3 (0-14) cycles	6.1 (5.0-8.0)	2.5 (1.9-3.8)	(59)

Table II. Continued.

Author, year	Phase	N	Median age, years (range)	Regimens	Dose	Route	Duration, median (range) or mean ± SD	Overall survival, months mean (95% CI)	Progression-free survival, months mean (95% CI)	(Refs.)
	1b/2	53	64 (49-82)	Gem+Vis	GDC-0449 150 mg daily		4 (1-12) cycles	6.9 (5.8-8.0)	4.0 (2.5-5.3)	
Ramanathan *et al*, 2016	3	430	63 (32-88)	Gem	Gem 1,000 mg/m^2 weekly for 7 of 8 weeks (cycle 1); in subsequent cycles, all patients were administered treatment on days 1, 8 and 15 every 4 weeks	IV		6.7 (6.0-7.2)	3.7 (3.6-4.0)	(60)
	3	431	62 (27-86)	Gem+Nab-p	Gem 1,000 mg/m^2 on days 1, 8, 15, 29, 36 and 43 + Nab-P 1+++25 mg/m^2	IV		8.5 (7.9-9.5)	5.5 (4.5-5.9)	

[a]Mean ± SD. SD, standard deviation; N/A, not applicable; b.i.d., twice daily; IV, intravenous; PO, per os; CI, confidence interval; Gem, gemcitabine; Axit, axitinib; 5-FU, 5-fluorouracil; Erl, erlotinib; Cap, capecitabine; Cet, cetuximab; Cis, cisplatin; Bev, bevacizumab; Eta, etanercept; Exa, exatecan; Iri, irinotecan; Mar, marismastat; Nab-p, nab-paclitaxel; Pem, pemetrexed; Radio, radiotherapy; Sor, sorafenib; Tip, tipifarnib; Vis, vismodegib; Oxa, oxaliplatin; Leu, leucovorin; Flu, fluorouracil.

Table III. Risk assessment of the included studies.

Author, year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of assessment	Incomplete outcome outcome data	Selective reporting	Otherbias	Total scores	(Refs.)
Cunningham *et al*, 2009	L	L	L	L	H	U	L	5	(30)
Conroy *et al*, 2005	U	H	L	L	L	U	L	4	(32)
Berlin *et al*, 2002	L	L	L	L	L	L	L	7	(41)
Bramhall *et al*, 2002	L	L	L	L	L	L	L	7	(42)
Rocha Lima *et al*, 2004	L	L	H	L	L	L	L	6	(43)
Van Cutsem *et al*, 2004	L	L	L	L	L	U	L	6	(44)
Oettle *et al*, 2005	L	L	L	L	L	L	L	7	(45)
Von Hoff *et al*, 2005	L	L	L	L	L	L	L	7	(46)
Abou-Alfa *et al*, 2006	L	L	L	L	L	L	L	7	(47)
Heinemann *et al*, 2006	L	L	L	L	L	L	L	7	(48)
Stathopoulos *et al*, 2006	L	L	L	L	L	L	L	7	(49)
Herrmann *et al*, 2007	L	L	L	L	H	L	L	6	(50)
Moore *et al*, 2007	L	L	L	L	H	L	L	6	(51)
Spano *et al*, 2008	L	L	L	L	L	L	L	7	(52)
Colucci *et al*, 2010	L	L	L	L	L	L	L	7	(40)
Philip *et al*, 2010	L	L	L	L	H	L	L	7	(53)
Kindler *et al*, 2011	L	L	L	L	L	L	L	7	(54)
Loehrer *et al*, 2011	L	L	L	L	L	L	L	7	(55)
Heinemann *et al*, 2012	L	L	L	L	L	L	L	7	(56)
Wu *et al*, 2013	L	L	L	L	L	L	L	7	(57)
Moehler *et al*, 2014	L	L	L	L	L	L	L	7	(58)
Catenacci *et al*, 2015	L	L	L	L	L	L	U	6	(59)
Ramanathan *et al*, 2016	L	L	L	L	H	L	L	6	(60)

L, low risk of bias; U, unclear risk of bias; H, high risk of bias.

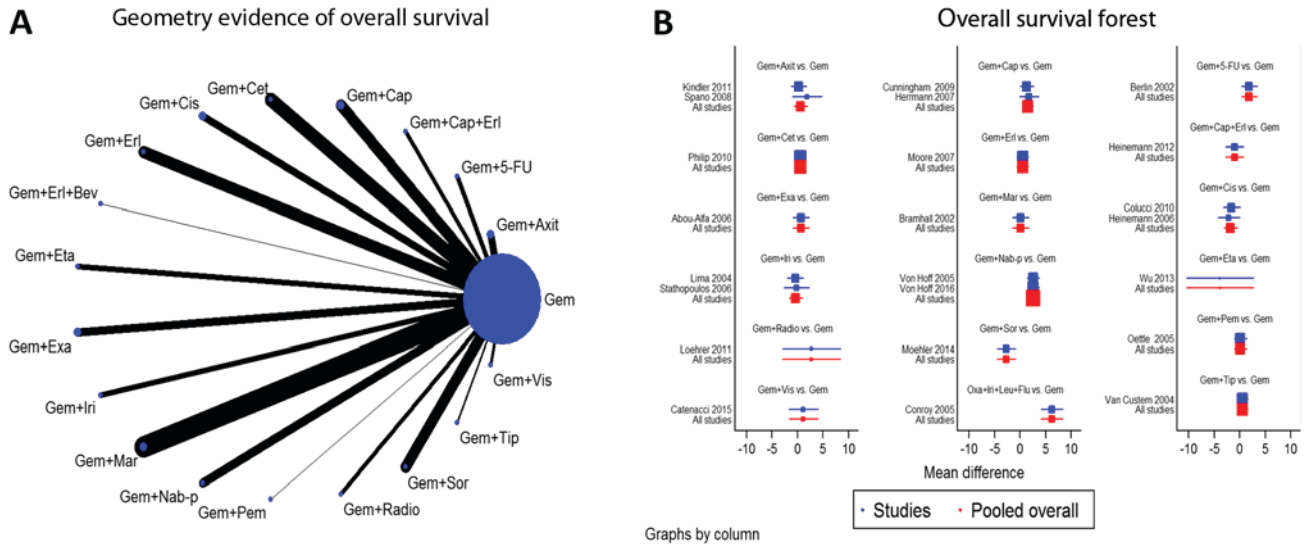

Figure 2. Network and forest plot for overall survival. (A) Geometry evidence of overall survival. (B) Overall survival forest. Gem, gemcitabine; Axit, axitinib; 5-FU, 5-fluorouracil; Erl, erlotinib; Cap, capecitabine; Cet, cetuximab; Cis, cisplatin; Bev, bevacizumab; Eta, etanercept; Exa, exatecan; Iri, irinotecan; Mar, marismastat; Nab-p, nab-paclitaxel; Pem, pemetrexed; Radio, radiotherapy; Sor, sorafenib; Tip, tipifarnib; Vis, vismodegib.

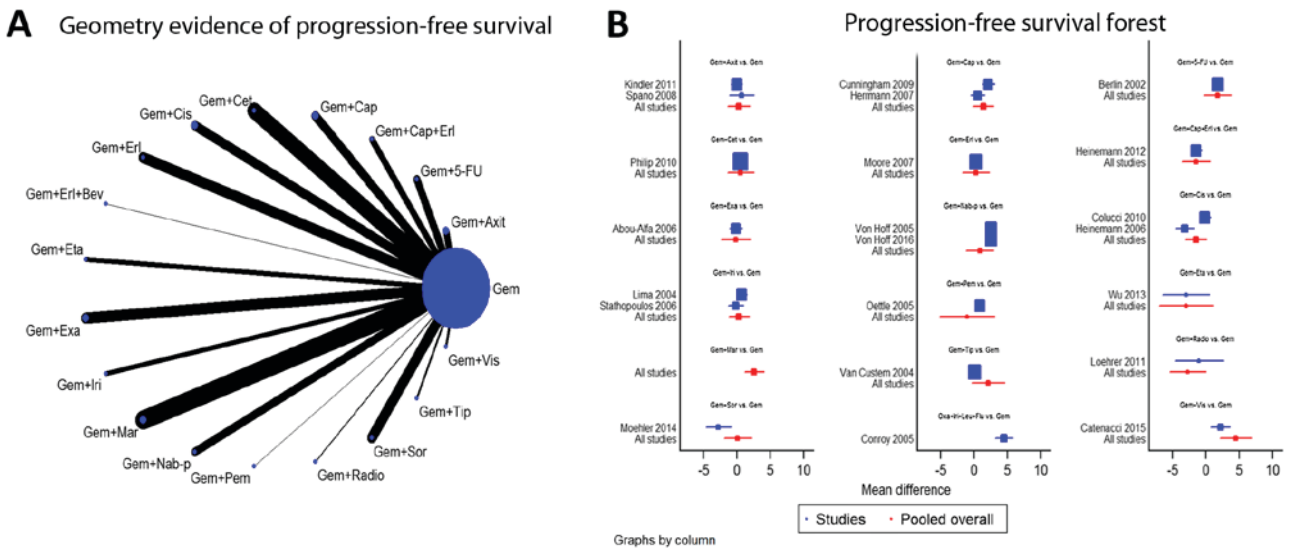

Figure 3. Network and forest plot for progression-free survival. (A) Geometry evidence of progression-free survival. (B) Progression-free survival forest. Gem, gemcitabine; Axit, axitinib; 5-FU, 5-fluorouracil; Erl, erlotinib; Cap, capecitabine; Cet, cetuximab; Cis, cisplatin; Bev, bevacizumab; Eta, etanercept; Exa, exatecan; Iri, irinotecan; Mar, marismastat; Nab-p, nab-paclitaxel; Pem, pemetrexed; Radio, radiotherapy; Sor, sorafenib; Tip, tipifarnib; Vis, vismodegib.

forest plots indicated the effectiveness of the different regimens compared with the pooled overall result (Figs. 2B and 3B).

Ranking treatments. Due to the variable conditions of APC, a critical aspect to be considered by medical doctors is what chemotherapy regimens are the most suitable and reasonable for the specific conditions of their patients. Therefore, 19 chemotherapy regimens were ranked according to their SUCRA probabilities based on OS and PFS (Fig. 4).

Regarding OS (Fig. 4A), Gem ranked 6th with a SUCRA value of 63.6. The top five combination regimens included Gem+radiotherapy (Radio), Gem+cisplatin (Cis), Gem+erlotinib (Erl)+bevacizumab (Bev), Gem+capecitabine (Cap)+Erl, and Gem+exatecan (Exa). The present results suggested that radiotherapy was the most effective treatment in extending the OS of patients, consistently with the results observed for PFS (Fig. 4B). The SUCRA scores for Gem+irinotecan (Iri) to Gem+tipifarnib presented a similar medium rank, and the scores for Gem+Cap to Gem+vismodegib (Vis) presented a low rank.

For PFS (Fig. 4B), Gem ranked 8th with a SUCRA value of 57.2. The top seven combination regimens included Gem+Radio, Gem+Erl+Bev, Gem+Cis, Gem+Cap+Erl, Gem+pemetrexed, Gem+Iri and Gem+etanercept. The SUCRA scores from Gem+ sorafenib (Sor) to Gem+ nab-paclitaxel (Nab-p) presented a medium rank, and Gem+Cap to Gem+Vis presented a low rank.

Adverse events. In addition to survival, health-associated quality of life issues are a central aspect for patients with

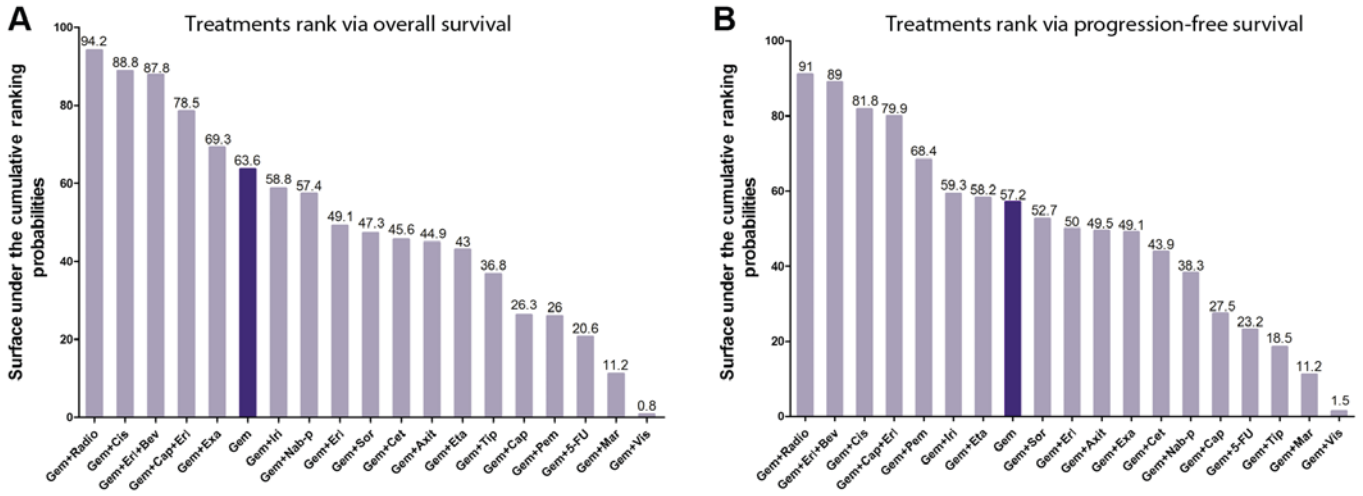

Figure 4. Treatment ranking by overall survival and progression-free survival. (A) Treatment ranking by overall survival. (B) Treatment ranking by progression-free survival. Gem, gemcitabine; Axit, axitinib; 5-FU, 5-fluorouracil; Erl, erlotinib; Cap, capecitabine; Cet, cetuximab; Cis, cisplatin; Bev, bevacizumab; Eta, etanercept; Exa, exatecan; Iri, irinotecan; Mar, marismastat; Nab-p, nab-paclitaxel; Pem, pemetrexed; Radio, radiotherapy; Sor, sorafenib; Tip, tipifarnib; Vis, vismodegib.

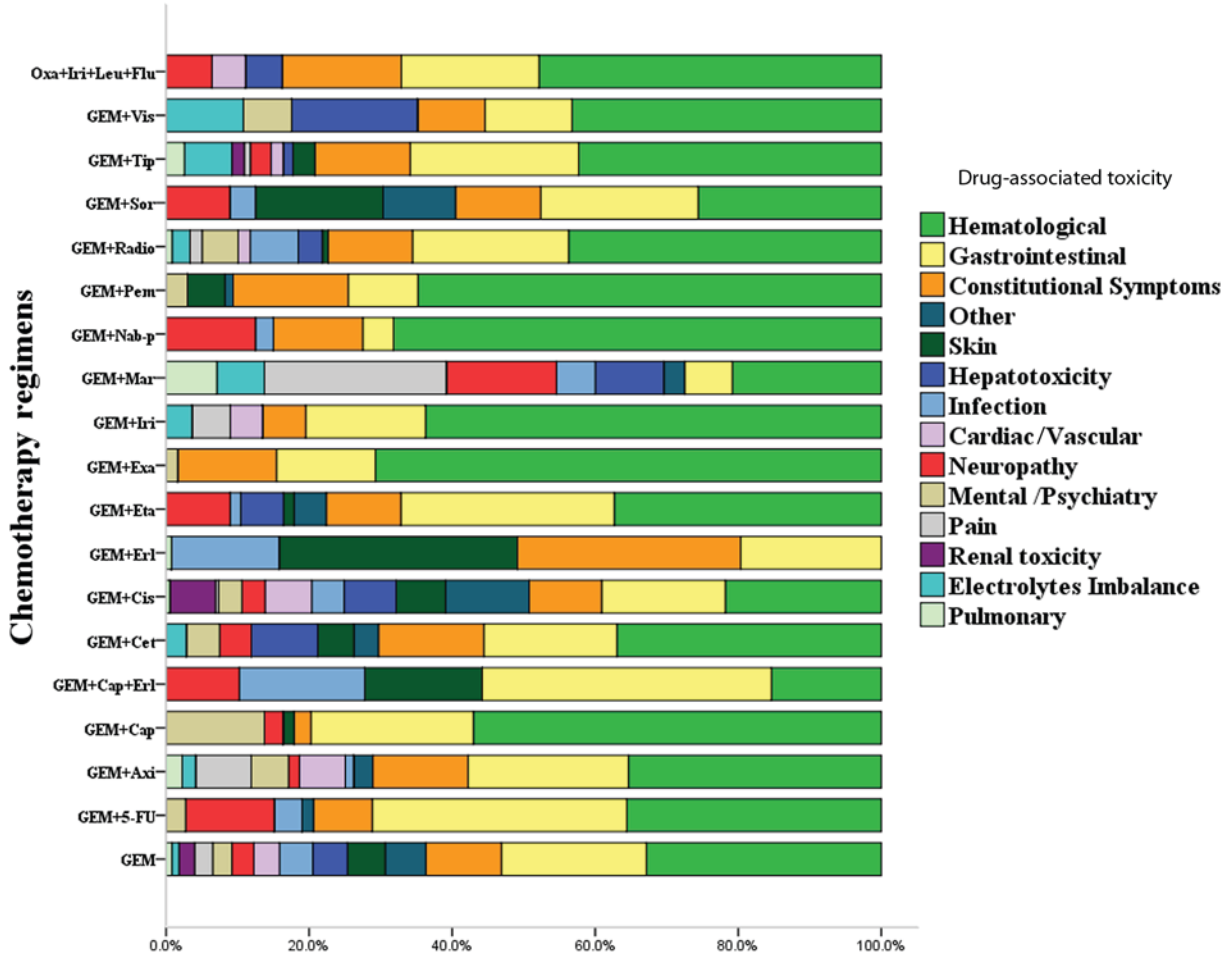

Figure 5. Assessment of the occurrence rates of 14 dominant drug-associated toxicities among 19 chemotherapy regimens. Gem, gemcitabine; Axit, axitinib; 5-FU, 5-fluorouracil; Erl, erlotinib; Cap, capecitabine; Cet, cetuximab; Cis, cisplatin; Bev, bevacizumab; Eta, etanercept; Exa, exatecan; Iri, irinotecan; Mar, marismastat; Nab-p, nab-paclitaxel; Pem, pemetrexed; Radio, radiotherapy; Sor, sorafenib; Tip, tipifarnib; Vis, vismodegib; Oxa, oxaliplatin; Leu, leucovorin; Flu, fluorouracil.

APC. Improving the health-associated quality of life by reducing treatment-associated toxicities and the occurrence rate of adverse events is important for patients. The majority of common treatment-associated toxicities include

'hepatotoxicity', 'haematological', 'mental/psychiatry', 'renal toxicity', 'gastrointestinal', 'neuropathy', 'electrolytes imbalance', 'pain', 'infection', 'skin', 'constitutional symptoms', 'cardiac/vascular', 'pulmonary' and 'other'. The majority of these toxicities seriously affect the quality of life of the patient during the treatment process.

Regarding the 19 chemotherapy regimens, each regimen may cause various treatment-associated toxicities, and the occurrence rate of each toxicity varied among treatments. Nevertheless, the three treatment-associated toxicities with the highest occurrence rates were 'haematological', 'gastrointestinal' and 'constitutional symptoms' for all regimens except Gem+Erl, which presented the largest proportions of toxicities. Furthermore, the remaining treatment-associated toxicities, including 'skin', 'hepatotoxicity', 'infection', 'cardiac/vascular', 'neuropathy', and 'mental/psychiatry', were the most common adverse effects among the majority of regimens, following 'haematological', 'gastrointestinal' and 'constitutional symptoms'. 'Renal toxicity', 'electrolytes imbalance' and 'pulmonary' presented the lowest occurrence rate among the regimens.

Treatment-associated toxicities always accompany the therapeutic process. To achieve the best results from the perspectives of the clinicians and the patients, patients must consider a series of unavoidable treatment-associated toxicities, leading to a complex selection process.

Discussion

Since Gem was approved as a first-line treatment for APC by the FDA in 1996, a number of combination chemotherapy regimens, including Gem+Xs, have emerged. Post-treatment long-term survival remains poor and is a marked risk of the current chemotherapy regimens (24). This issue may be caused by a failure of local control and of diagnosing localized APC in time (25). Associated RCTs and studies published between 2002 and 2016, covering a total of 14 years, were selected to assess the advantages and disadvantages of each regimen compared with Gem monotherapy.

Among the chemotherapy regimens, Gem+Radio presented the principal improvement in extending OS and PFS. This finding suggested that radiotherapy may block the progressive deterioration associated with advanced cancer and is consistent with the previous study of Youl *et al* (26), which identified that a gross tumor volume <48 cm^3 may be successfully targeted with radiotherapy. An additional three regimens, Gem+Cis, Gem+Erl+Bev and Gem+Cap+Erl, were better compared with Gem monotherapy in terms of OS and PFS. Regarding other combination regimens, Gem+Iri, Gem+Sor, Gem+Erl, Gem+Axitinib, Gem+Exa, Gem+Cetuximab, Gem+Nab-p and Gem+Cap presented higher SUCRA probabilities compared with Gem+5-FU, another double regimen. In contrast, Gem+marismastat and Gem+Vis exhibited decreased SUCRA probabilities. Although numerous regimens are available, side effects always accompany the therapeutic effect. Therefore, selecting the regimen that may offer the longest survival is a complex process that requires the clinician to comprehensively assess the disease status of the patient in order to identify a balance between the benefits and risks of the treatment.

A previous study demonstrated that patients who undergo 5-FU and 5-FU-based regimens following resection had improved survival rates (27). 5-FU has been used as the principle chemoradiation and/or chemotherapy regimens and was previously considered the principal effective chemotherapeutic agent available in pancreatic cancer treatment. In the 1990s, Gem was first demonstrated to be a safe drug with low toxicity for APC treatment (28). Subsequent clinical trials demonstrated the significant advantages of Gem for short-term and long-term OS in the treatment of advanced and metastatic pancreatic cancer (8,29,30); these previous results demonstrated the effectiveness of Gem therapy in pancreatic cancer.

In patients with optimal performance status, concurrent chemotherapy, including FOLFIRINOX, albumin-bound paclitaxel and 5-FU, in combination with Gem, or other Gem-based combined chemotherapies, may provide increased survival benefits (31,32). Although patients at similar disease-stages receive the same chemical regimens, there may be various outcomes due to individual variations.

Gem has been the standard for treating APC since 1996, providing a limited survival of 6 months due to the intrinsic capacity of cancer cells and the surrounding microenvironment to resist cytotoxicity (33,34). Combination therapies with Gem have presented limited effectiveness in clinical trials, and the identification of novel therapeutic strategies that may increase median survival and PFS with reduced adverse effects, is required. Certain treatments, including 5-FU monotherapy, presented significantly decreased survival compared with Gem monotherapy and have demonstrated the effectiveness of Gem as a first-line chemotherapy for APC. Although certain trials examining combination therapies demonstrated improved objective response rates, the treatments failed to achieved improvement in all three of the most common outcomes measured; Median survival, PFS and the objective response rate (35-39). The present network meta-analysis of patients with unresectable pancreatic cancer suggested that the current median survival for patients treated with Gem was >6 months, and the objective response rate for Gem ranged between 4.4 and 17.3% (40). These results may represent the standard to be compared with future results of single-arm phase II trials involving Gem-based combination regimens. The severity of the adverse effects among these regimens was assessed by inconsistent scales, which may contribute to bias. Future studies may consider a consistent scale among various conditions in order to avoid possible biases.

In conclusion, numerous chemotherapy regimens are used to extend the survival and reduce the treatment-associated toxicities of patients with APC. The effect and treatment-associated toxicities of a particular regimen requires consideration to balance the benefits and risks for the patient. The present study provides additional evidence for selecting appropriate treatments according to the clinical situation.

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Availability of data and materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Authors' contributions

JC, FX and SY conceived and designed the present study. YX, LC, JY, XW, ZZ and NL performed the data extraction. JY and FX ensured the quality of the data. FX and SY analyzed the data. JC, FX and LC drafted the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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