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Review

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Folfirinox vs. Gemcitabine + Nab-Paclitaxel as the First-Line Treatment for Pancreatic Cancer: A Systematic Review and Meta-Analysis

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Abstract

Background: The efficacy and safety of Folfirinox (FFX) or gemcitabine + nab-paclitaxel (GnP) to be used as the first-line drugs for pancreatic cancer (PC) is yet to be established. We conducted an analysis of retrospective studies to assess the efficacy and safety of these two regimens by comparing their survival and safety outcomes in patients with PC.

Methods: We conducted an extensive review of two electronic databases from inception till February 2023 to include all the relevant studies that compared FFX with GnP published and unpublished work. Retrospective studies were only included. Overall survival (OS) and progression-free survival (PFS) were pooled using hazard ratios (HRs), while objective response rate (ORR) and safety outcomes were pooled using odds ratios (ORs) with 95% confidence interval (CI) using the random effects model.

Results: A total of 7,030 patients were identified in a total of 21 articles that were shortlisted. Pooled results concluded that neither FFX nor GnP was associated to increase the OS time (HR: 0.93, 95% CI: 0.83 - 1.04; P = 0.0001); however, FFX was more likely associated with increased PFS when compared to GnP (HR: 0.88, 95% CI: 0.81 - 0.97; P < 0.0001). ORR proved to be non-significant between the two regimens (OR: 0.90, 95% CI: 0.64 - 1.27; P = 0.15). Safety outcomes included neutropenia, anemia, thrombocytopenia and diarrhea. GnP was more associated with diarrhea (OR: 1.96, 95% CI: 1.22 - 3.15; P = 0.001), while FFX was seen to cause anemia (OR: 0.70, 95% CI: 0.51 - 0.98; P = 0.10) in PC patients. Neutropenia and thrombocytopenia were in-significant in the two drug regimens (OR: 1.10, 95% CI: 0.92 - 1.31; P = 0.33 and OR: 0.83, 95% CI: 0.60 - 1.13; P = 0.23, respectively).

Conclusion: FFX and GnP showed a significant difference in increasing the PFS, while no difference was observed while measuring OS. Safety outcomes showed that FFX and GnP shared similar safety profiles as FFX was associated with hematological outcomes, while GnP was more associated with non-hematological outcomes.

Keywords: Folfirinox; Gemcitabine + nab-paclitaxel; Pancreatic cancer; Overall survival; Progression-free survival; Objective response rate

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Introduction

Pancreatic cancer (PC) is considered as the root cause of cancer-related deaths worldwide with poor prognosis and lowest 5-year survival outcome [1, 2]. Thirty to forty percent of people are diagnosed after the age of 75 years with median age of diagnosis falling at 70 years [3-5]. Since 1990s numerous attempts have been made to treat PC [6-8]. After the conduction of two large scaled trials, two drug regimens have been introduced to treat PC as the first-line treatment.

The gemcitabine + nab-paclitaxel (GnP) combination was initiated in the market after its promising effects on the overall survival (OS) and progression-free survival (PFS) when compared to the gemcitabine monotherapy in the MPACT trial (Fig. 1) [7]. Similarly, PRODIGE4/ACCORD11 trial introduced Folfirinox (FFX), a combination of 5-fluorouracil (5-FU), leucovorin, oxaliplatin, and irinotecan, which showed significant results with regards to survival rates and benefits in contrast to gemcitabine being used alone [9]. As a conse-

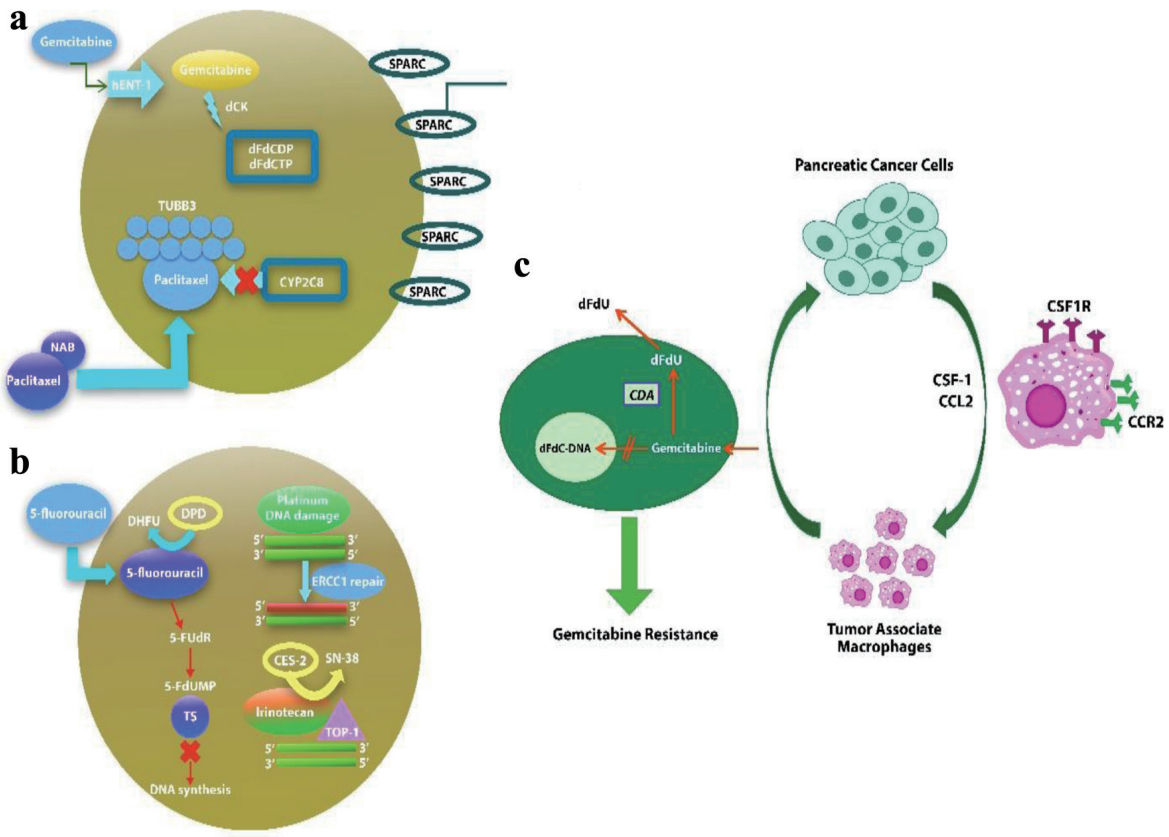

Figure 1. Potential biomarkers in nab-paclitaxel/gemcitabine (a), Folfirinox (b) regimens of drug metabolism and mechanism of action. (c) Macrophages induce gemcitabine resistance by up-regulation of CDA.

quence, two regimens are now in market to be used as first-line drugs to treat PC.

Despite the introduction of the two regimens, there is a lack of data when comparing the two combinations exclusively with respect to OS, PFS and objective response rate (ORR). As concluded by a previous meta-analysis, the two regimens had no association in increasing the OS, PFS or ORR. Furthermore, the previous studies did not evaluate the detailed safety profiles for the two regimens; hence, our meta-analysis, with a larger sample size and excellent statistical power, examined the safety profiles and included the most recent published studies. Importantly, the literature search period for our study extends until February 2023; therefore, our study encompasses recently published randomized controlled trials (RCTs), which were conducted to fill in the literature gap [10]. Lastly, our study has different clinical implications based on patient settings. In practice, FFX is often recommended for younger patients, while GnP is typically preferred in older patients. This aspect adds another layer of complexity in the direct comparison of these two regimens, which was duly considered in our study [11, 12]. We conducted this meta-analysis and systematic review to rule out all the in-indifferences and find the best therapy in regard to efficacy and toxicity to be used as first-line treatment for PC in all age groups.

Materials and Methods

Data sources and search strategy

This meta-analysis was conducted in accordance to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [13]. A comprehensive review of the two electronic databases was conducted from inception till February 2023 independently by two researchers which included MEDLINE and Cochrane Central incorporating articles written in English only. We utilized the following search string: (Metastatic Pancreatic cancer OR Pancreatic carcinoma OR Pancreatic cancer OR Pancreatic tumor OR Pancreatic neoplasm OR Pancreatic adenocarcinoma OR Pancreatic adenoma) AND (Fluorouracil OR Leucovorin OR Irinotecan OR Oxaliplatin OR Folfirinox OR Folfirinox) AND (Gemcitabine plus nab-paclitaxel OR GnP OR albumin bound paclitaxel OR Gemcitabine) AND (Progression free survival OR Overall survival OR OS OR PFS OR Toxicity). In addition, generic and trade names were used to screen any published or unpublished work at [14, 15] that could have been left out. Lastly, grey literature and reference list from past meta-analysis were manually reviewed to rule out the chances of missing any study (Supplementary Material 1, www.wjon.org).

Study selection

The eligibility criteria to shortlist the studies were as follows: 1) Retrospective studies published in English; 2) Studies conducted on human species; and 3) Studies reporting adverse effects or safety in either metastatic PC or locally advanced metastatic cancer. The standard dose of FFX included oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, irinotecan 180 mg/m^2,5-FU bolus 400 mg/m^2 and 5-FU 2,400 mg/m^2. Case reports, case series and meta-analysis were left out with duplicates to remove any inaccuracies.

Data extraction and assessment of study quality

Our systematic search was supplemented by a manual search with results being exported to MENDLEY reference library to pull out any duplicates. The left-over studies were assessed carefully by two independent researchers (NM and SD). The inclusion of the study was made on the lines of previously defined criteria, while a third reviewer was consulted AN to resolve any discrepancies. Studies were shortlisted first on the basis of their title and abstract after which a full text review was given to confirm its inclusion. From the final list of studies, primary outcome of OS and PFS was extracted along with any grade adverse events (according to the National Cancer Institute Common Terminology Criteria for Adverse events) including hematological and non-hematological outcomes such as neutropenia, thrombocytopenia, anemia and diarrhea.

Statistical analysis

Review manager version 5.4.1 was used to conduct all the statistical analysis. The results were pooled as hazard ratios (HRs) for OS and PFS, while odds ratios (ORs) were used to pool the results for ORR and adverse events (AEs) with a 95% confidence interval (CI) using the random effects model. Forest plots were made to evaluate the results. Heterogeneity across all the studies was based on the Higgins I^2 statistics with I^2 = 25-50% considered mild, I^2 = 50-75% moderate and I^2 > 75% severe heterogeneity. Visual screening of the funnel plots was done to eradicate publication bias. A P-value of less than 0.05 was considered to be significant in all the cases.

Results

Literature search results

Our initial search of two electronic databases yielded a total of 1,127 potentially relevant articles. After screening and exclusion of articles, 21 studies remained for synthetic analysis. Our analysis included a total of two drugs of FFX and GnP. PRISMA flow chart below summarizes the results of our literature search (Supplementary Material 2, www.wjon.org). Graphical representation of the study in a systematic way is shown in Supplementary Material 3 (www.wjon.org).

Study characteristics, sample demography, and quality assessment

A total of 7,030 patients were found in the shortlisted studies with 3,653 patients in the FFX group while 3,377 patients in the GnP group. Median follow-up duration of studies ranged from 4.1 to 33 months. The relevant study and patient characteristics are found in Table 1 while Table 2 shows the demographic details [16-36]. Table 3 shows the study criteria and guidelines [16-36]. All the studies included had high quality. A comprehensive quality assessment of each study is presented in Supplementary Material 4 (www.wjon.org). The tumor locations are presented in Supplementary Material 5 (www.wjon.org).

OS

A total of 18 studies [16-33] reported OS out of the 21 relevant studies. There was no statistical difference found in between the usage of FFX and GnP as first-line treatment to increase the OS time (HR: 0.93, 95% CI: 0.83 - 1.04; P = 0.0001) (Fig. 2a, b). Sensitivity analysis was conducted and studies with different guidelines were removed, although no significant difference was observed in the results (HR: 0.91; 95% CI: 0.81 - 1.01; P = 0.005) (Supplementary Material 6, www.wjon.org).

PFS

A total of 13 studies [16-22, 24, 25, 27, 29, 32, 34] reported PFS and a significant difference was observed between the use of FFX and GnP as the first-line treatment for PC (HR: 0.88, 95% CI: 0.81 - 0.97; P < 0.0001) (Fig. 3a, b). Sensitivity analysis was conducted and removal of studies yielded a non-significant result (HR: 0.93, 95% CI: 0.85 - 1.02; P = 0.04) (Supplementary Material 7, www.wjon.org).

ORR

Seven studies [16, 20, 25, 27, 32, 34, 35] reported ORR with a total of 1,274 patients. There were 556 patients in the FFX arm, while 718 patients in the GnP arm. No statistical difference was observed between the use of two drugs (OR: 0.90; 95% CI: 0.64 - 1.27; P = 0.15) (Fig. 4a, b).

Hematological outcomes

Anemia

Ten studies [16, 17, 19, 22, 28-30, 33, 34, 36] reported anemia as an AE with a total of 2,379 patients. There were 1,136 in the FFX arm, while 1,243 in the GnP arm. A statistical difference was observed as anemia was observed more in the FFX arm as compared to the GnP group (OR: 0.70, 95% CI: 0.51 - 0.98; P = 0.10) (Fig. 5a, b).

Table 1. Study and Patient Characteristics

Author	Year of publication	Country	Start time	End time	PS	Number of patients	Median age	Males (%)	Median follow-up	Treatment
Nakazawa et al [32]	2019	Japan	2013.12	2018.6	0 - 2	92	68	NA	14.9 months (0.7 - 30.9)	GEM-NAB
						119	61	NA	13.1 months (1.3 - 40.8)	Folfirinox
Kim et al [29]	2018	USA	2015.4	2015.12	0 - 4	337	64.59	64.7%	10.7 months	GEM-NAB
						317	59.03	67.2%		Folfirinox
Muranaka et al [34]	2017	Japan	2013.12	2015.9	0 - 1	22	66.5	54.5%	8.3 months	GEM-NAB
						16	63	62.5%	11.9 months	Folfirinox
Papneja et al [33]	2019	Canada	2011	2016	0 - 3	33	64	52%	8 months	GEM-NAB
						86	59	62%		Folfirinox
Cho et al [35]	2018	Korea	2015	NA	NA	81	54	NA	7.9 months (1.5 - 23.4)	GEM-NAB
						86	65	NA		Folfirinox
Williet et al [24]	2019	France	2015.6	2018.6	0 - 2	109	68.1	49.5%	NA	GEM-NAB
						107	61.8	59.8%		Folfirinox
Chan et al [27]	2019	Canada	2015.4	2017.3	NA	498	69.14	60.2%	NA	GEM-NAB
						632	61.83	54.6%		Folfirinox
Barrera et al [26]	2019	Canada	2010	2018	NA	41	NA	NA	NA	GEM-NAB
						60	NA	NA		Folfirinox
						60	NA	NA		GEM
Longo Munoz et al [31]	2019	Spain	2011.1	2018.5	NA	NA	NA	NA	NA	GEM-NAB
Chun et al [28]	2021	Korea	2011.5	2019.3	0 - 2	151	64	60.3%	33 months	GEM-NAB
						151	62	55.6%		Folfirinox
Rapposelli et al [19]	2021	NA	2014.1	2020.12	0 - 2	268	62	61.9%	21.8 months	GEM-NAB
						171	61	62%		Folfirinox
Lee et al [30]	2020	South Korea	2011.7	2017.12	0 - 2	181	69	53%	NA	GEM-NAB
						232	60	61%		Folfirinox
Riedl et al [20]	2021	Austria	2010.8	2019.10	0 - 1	297	70	59%	26.2 months	GEM-NAB
						158	63	59%		Folfirinox
Sigel et al [23]	2022	NA	2003	2016	NA	317	66	98%	NA	GEM-NAB
						353	61	94%		Folfirinox
Ay et al [17]	2022	NA	2010.1	2020.12	0 - 1	79	61	49.4%	NA	GEM-NAB
						103	58	60.2%		Folfirinox
Santucci et al [21]	2022	Australia and New Zealand	2016	2020	0 - 4	375	67	52.7%	8.7 months	GEM-NAB
						73	59	60.3%	6.3 months	Folfirinox
Yoshida et al [25]	2022	Japan	2001.4	2017.12	0 - 2	28	62.5	57.1%	9.4 months	GEM-NAB
						10	56.5	90%		Folfirinox
Pijnappel et al [18]	2022	Netherlands	2015	2018	0 - 4	207	69	50%	4.1 months	GEM-NAB
						1029	62	54%		Folfirinox
Arima et al [16]	2021	Japan	2013.12	2017.3	0 - 2	47	68	61.7%	14.2 months	GEM-NAB
						16	65	56.3%		Folfirinox
Templeton et al [36]	2020	Canada	2011	2017	0 - 1	10	66.9	70%	15 months	GEM-NAB
						10	62.6	70%		Folfirinox
Servetto et al [22]	2022	Italy	2011.2	2020.11	0 - 1	117	63.7	57.3%	NA	GEM-NAB
						43	53.6	65.1%		Folfirinox

USA: United States of America; PS: performance status; NA: not applicable; GEM-NAB: gemcitabine + nab-paclitaxel.

Table 2. Demographic Details of the Study and Patient Characteristics

Author	GEM-NAB		Folfirinox		GEM-NAB			Folfirinox		
	Male	Female	Male	Female	Head	Body	Tail	Head	Body	Tail
Chun et al [28]	91	60	84	67	33	-	-	37	-	-
Rapposelli et al [19]	166	102	106	65	105	83	70	67	53	45
Lee et al [30]	96	85	141	91	63	52	55	85	59	73
Riedl et al [20]	174	123	94	64	175	57	39	74	38	32
Sigel et al [23]	312	5	333	20	-	-	-	-	-	-
Ay et al [17]	39	40	62	41	-	-	-	-	-	-
Santucci et al [21]	198	178	44	29	209	80	70	40	14	16
Chan et al [27]	300	198	345	287	-	-	-	-	-	-
Yoshida et al [25]	16	12	9	1	-	-	-	-	-	-
Pijnappel et al [18]	104	103	556	473	80	46	49	393	212	270
Arima et al [16]	29	18	9	7	-	-	-	-	-	-
Templeton et al [36]	7	3	7	3	9	1	-	8	2	-
Servetto et al [22]	67	50	28	15	62	-	-	17	-	-
Nakazawa et al [32]	-	-	-	-	-	-	-	-	-	-
Kim et al [29]	218	119	213	104	170	93	82	163	83	74
Muranaka et al [34]	12	10	10	6	-	-	-	-	-	-
Papneja et al [33]	17	16	53	33	24	6	2	50	13	18
Cho et al [35]	-	-	-	-	-	-	-	-	-	-
Williet et al [24]	54	55	64	43	51	28	30	47	26	34
Barrera et al [26]	-	-	-	-	-	-	-	-	-	-
Longo Munoz et al [31]	-	-	-	-	-	-	-	-	-	-

GEM-NAB: gemcitabine + nab-paclitaxel.

Neutropenia

A total of 13 studies [16, 17, 19, 20, 22, 23, 28-30, 32-34, 36] with 3,713 patients reported neutropenia with 1,764 patients in the FFX group while 1,949 patients in the GnP group. The results were non-significant; hence, there was no difference seen between the two regimens in causing neutropenia (OR: 1.10; 95% CI: 0.92 - 1.31; P = 0.33) (Fig. 6a, b).

Thrombocytopenia

Ten studies [16, 17, 19, 22, 28-30, 32, 34, 36] reported thrombocytopenia with a total of 2,369 patients with 1,126 in FFX group in contrast to 1,243 in the GnP group. There was no statistical significance seen in the two drug choices that caused thrombocytopenia (OR: 0.83; 95% CI: 0.60 - 1.13; P = 0.23) (Fig. 7a, b).

Non-hematological outcomes

Diarrhea

A total of 12 studies [16, 17, 19, 20, 22, 23, 29, 30, 32-34, 36] reported diarrhea as an AE with a total of 3,421 patients. A total of 1,616 patients were recorded in the FFX group and 1,807 patients in the GnP group. The results were significant as diarrhea was observed more in the GnP group when compared to FFX (OR: 1.96; 95% CI: 1.22 - 3.15; P = 0.001) (Fig. 8a, b).

Discussion

Our meta-analysis of more than 7,000 patients evaluated the efficacy and safety of two drug regimens, FFX and GnP, as the first-line treatment for advanced and metastatic PC (Fig. 1). As summarized in numerous trails and studies, our analysis also showed no statistical difference in increasing the OS time [10, 16, 19-23, 25, 29, 37]. Although previous meta-analyses have shown no significant difference in the survival outcomes of these drugs, this is the first study which showed a statistically significant increase in the PFS with use of FFX as the first-line treatment. Safety was evaluated in various trials and studies along with efficacy. Differences were found in safety profile of using these drugs with FFX being more associated with anemia while diarrhea occurred more in patients who used GnP.

Our study evaluated the OS time and the results were consistent with the previous meta-analysis and studies that used FFX and GnP as first-line treatments for PC, although five

Table 3. Study Criteria and Guidelines

Author	Guidelines	Safety criteria
Chun et al [28]	Good Clinical Practice guidelines and the Declaration of Helsinki	CTCAE
Rapposelli et al [19]	Good Clinical Practice guidelines and the Declaration of Helsinki	CTCAE
Lee et al [30]	NA	CTCAE
Riedl et al [20]	Local and National guidelines	NA
Sigel et al [23]	Declaration of Helsinki	NA
Ay et al [17]	Declaration of Helsinki	CTCAE
Santucci et al [21]	Declaration of Helsinki	NA
Chan et al [27]	NA	NA
Yoshida et al [25]	The Declaration of Helsinki	NA
Pijnappel et al [18]	Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines	NA
Arima et al [16]	The Declaration of Helsinki	CTCAE
Templeton et al [36]		
Servetto et al [22]	Good Clinical Practice guidelines and the Declaration of Helsinki	CTCAE
Nakazawa et al [32]	NA	NA
Kim et al [29]	NA	NA
Muranaka et al [34]	The Declaration of Helsinki	CTCAE
Papneja et al [33]	NA	NA
Cho et al [35]	NA	NA
Williet et al [24]	The Declaration of Helsinki	National Cancer Institute CTCAE
Barrera et al [26]	NA	NA
Longo Munoz et al [31]	NA	NA

CTCAE: Common Terminology Criteria for Adverse Events; NA: not available.

studies have shown that FFX is likely to be associated with a longer OS when compared to GnP [17, 18, 27, 28, 38]. There was no statistical difference found with a longer PFS with the use of FFX or GnP but pooling of studies and a larger number of participants from previous meta-analysis showed that FFX was associated with a longer PFS in contrast to GnP [10]. Safety profiles have differed between the two regimens with a difference of results in multiple studies. Two studies suggested the use of GnP as the first-line treatment due to its reduced cost and AEs while one study suggested that FFX has better survival and safety outcomes hence it should be the drug of choice for PC [29, 33, 35]. Furthermore, our study showed a statistical difference with anemia being more likely to be associated with FFX while diarrhea being associated with GnP. Our results differed from another study which suggested that FFX was more associated with diarrhea while FFX was more likely to cause anemia [19]. ORR was found to be statistically significant in the previous meta-analysis but pooling individual studies showed no statistical difference in ORR between the two regimens [10].

Previous studies have shown to differ in their choice of drug to be used as a first-line treatment in PC. Although studies have concluded that using FFX is likely to be associated with increased OS and PFS but due to a smaller testing sample size, a firm relation is yet to be established. As FFX is a combination of drugs, a larger sample population can shift the tables towards the use of FFX as the first-line drug. Irinotecan, a drug in the combination, has shown to exert its specific and synergistic effects on metastatic PC along with 5-FU and calcium folinate [39-42]. Furthermore, a trial concluded that oxaliplatin produced its clinical effects on PC only when it was used in combination with 5-FU [43]. Lastly a clinical trial summarized that use of irinotecan, oxaliplatin, 5-FU, and calcium leucovorin together can produce clinical benefits in patients with PC [44]. On the other hand, toxicities of any drug cannot be ignored. FFX is associated with hematological toxicities due to the mechanism of action of drug itself. Previous studies have shown that use of oxaliplatin as an anticancer agent has caused bone marrow suppression and blood system toxicities such as thrombocytopenia [45]. In contrast GnP is considered as a much safer option as summarized by two studies, hence GnP is considered to be safer when it comes to hematological safety outcomes [29, 35].

Considering the implications and cause of heterogeneity, we should keep in mind that the selection of these drugs to be used in patients as first-line treatment for PC depends on several factors that ultimately contribute to its efficacy. Such factors include socio-economic status, ethnicity, ECOG performance score, age, baseline characteristics and comorbidities. In MPACT trial, use of GnP showed a longer survival in Asian subgroup when compared to the western subgroup [46]. In addition, a meta-analysis showed that Asian subgroup had

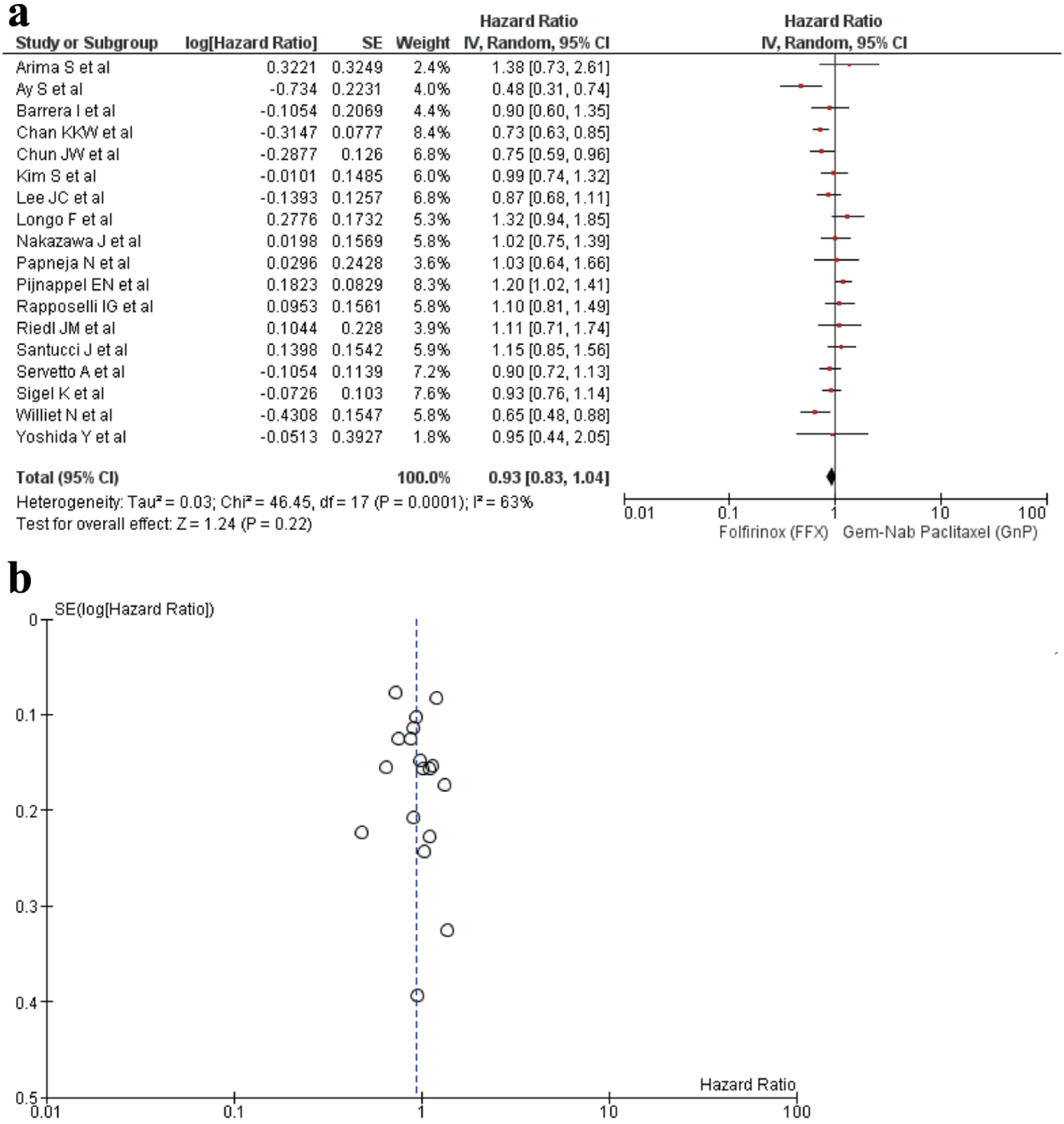

Figure 2. (a) Forest plot of OS (HR: 0.93; 95% CI: 0.83 - 1.04; P = 0.0001). (b) Funnel plot of OS. HR: hazard ratio; CI: confidence interval; OS: overall survival.

more intense AEs as compared to the western subgroup [47]. Hence it can be concluded that non-uniformity in the ethnicity of patients could be a possible factor for heterogeneity.

In our study, there were some limitations that need to be addressed. Randomization of patients based on demographic factors, ethnicity, baseline characteristics, age and comorbidities could not be possible as retrospective studies were only included in this analysis. Furthermore, due to a relatively small sample size, the results might have been overestimated leading to biasness. The patients differed in their baseline characteristics owing to an overall biasness and heterogeneity when recording up AEs. Lastly due to incomplete follow-up, poten-

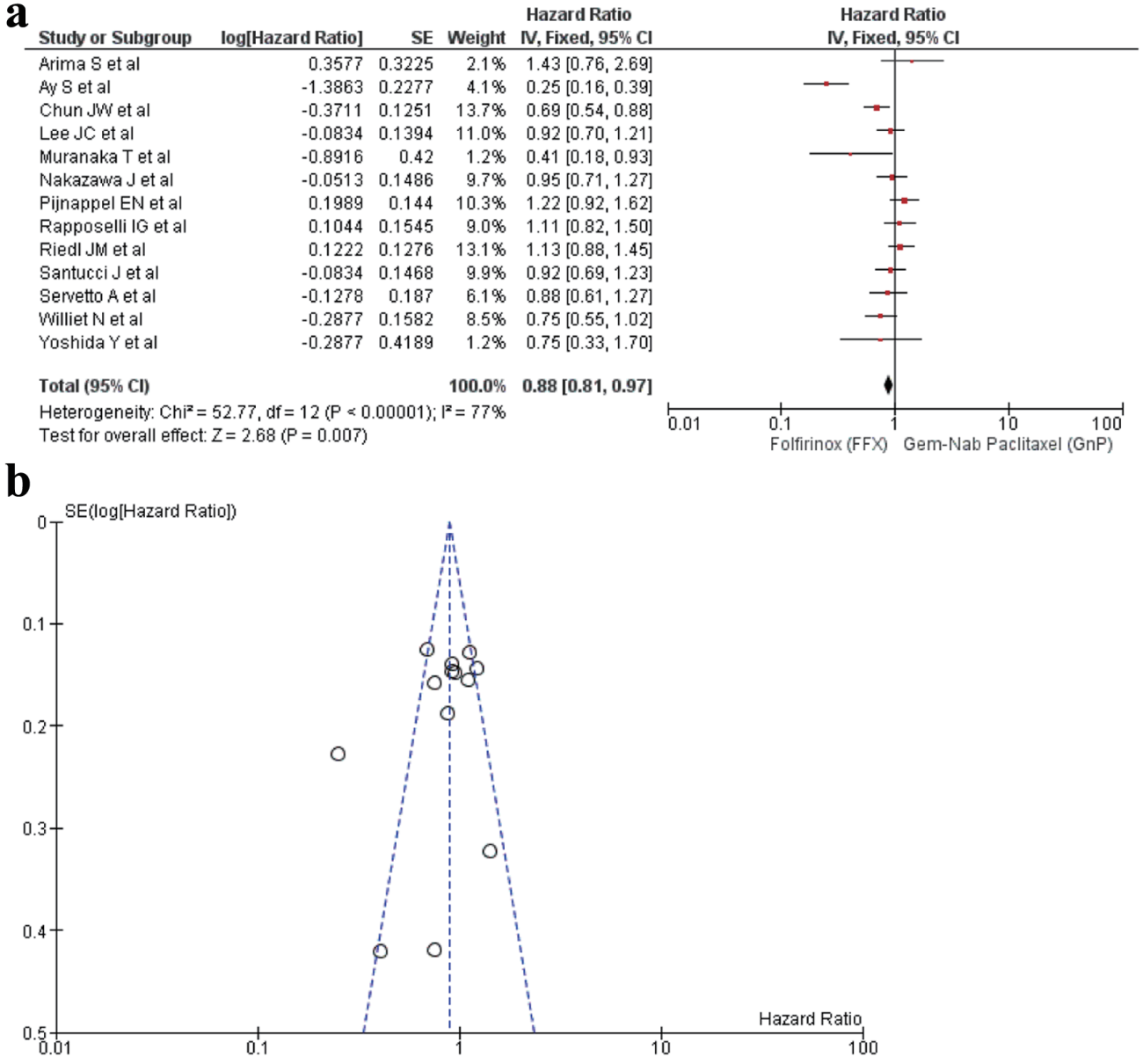

Figure 3. (a) Forest plot of PFS (HR: 0.88; 95% CI: 0.81 - 0.97; P < 0.0001). (b) Funnel plot of PFS. PFS: progression-free survival; HR: hazard ratio; CI: confidence interval.

tial biasness in the calculation of PFS and OS could not be avoided. Nevertheless, we analyzed the efficacy and safety of two regimens on a larger sample size from the previous meta-analysis and tried our best to include propensity-matched data to eradicate any biasness and heterogeneity.

Conclusion

FFX is more associated with prolonging PFS, while no difference is seen in OS of patients that used FFX or GnP as the first-line drug. AEs or toxicities are a key factor to determine the use of any drug for a particular disease, hence with FFX being more associated with hematological outcomes while GnP being more likely to be associated with non-hematological outcomes, there is a dire need for future trials to be conducted on a large sample size population to determine the drug of choice to be used as first-line treatment for PC.

Supplementary Material

Suppl 1. PubMed - detailed search strategy.

Suppl 2. PRISMA flow diagram for retrieval of articles.

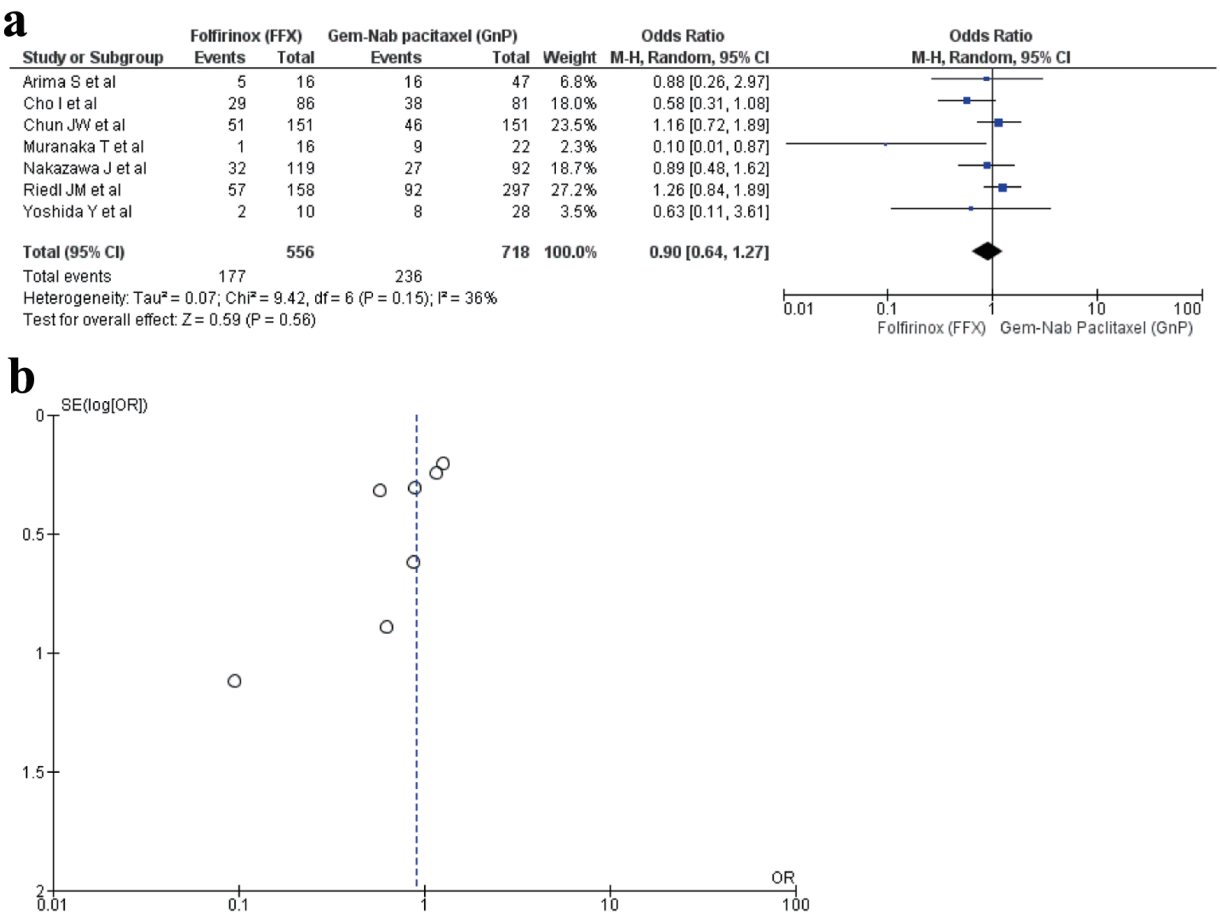

Figure 4. (a) Forest plot of objective response rate (OR: 0.90; 95% CI: 0.64 - 1.27; P = 0.15). (b) Funnel plot of objective response rate. OR: odds ratio; CI: confidence interval.

Suppl 3. Graphical representation of the study in a systematic way.

Suppl 4. Quality assessment of articles performed through QUADS-2 tool.

Suppl 5. (A) Distribution of tumor locations in pancreatic head, body, and tail. Series 1 and 2 show the prevalence of tumors within different pancreas regions. (B) Distribution of tumor locations in pancreatic head, body, and tail. Series 1 and 2 depict the spatial distribution and prevalence of tumors within different pancreas regions.

Suppl 6. (A) Forest plot of overall survival (OS) sensitivity analysis (HR: 0.91, 95% CI: 0.81 - 1.01; P = 0.005). (B) Funnel plot of OS sensitivity analysis.

Suppl 7. (A) Forest plot of progression-free survival (PFS) sensitivity analysis (HR: 0.93, 95% CI: 0.85 - 1.02; P = 0.04). (B) Funnel plot of PFS sensitivity analysis.

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None to declare.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contributions

Nooraldin Merza, Sabeeh Khawar Farooqui, Sophia Haroon Dar, and Tony Varughese: manuscript writing, an overview of the previously published works on a topic. Rehmat Ullah Awan, Lamaan Qureshi, and Saad Ali Ansari: database extraction, results, and statistics. Saad Ali Ansari and Jamie Mcilvaine: manuscript preparation and editing. Hadi Qureshi: data collection, manuscript preparation, and editing content. Ali Nawras, Yaseen Alastal, and Mona Hassan: drafting and approval of final version, manuscript review, critical revision of

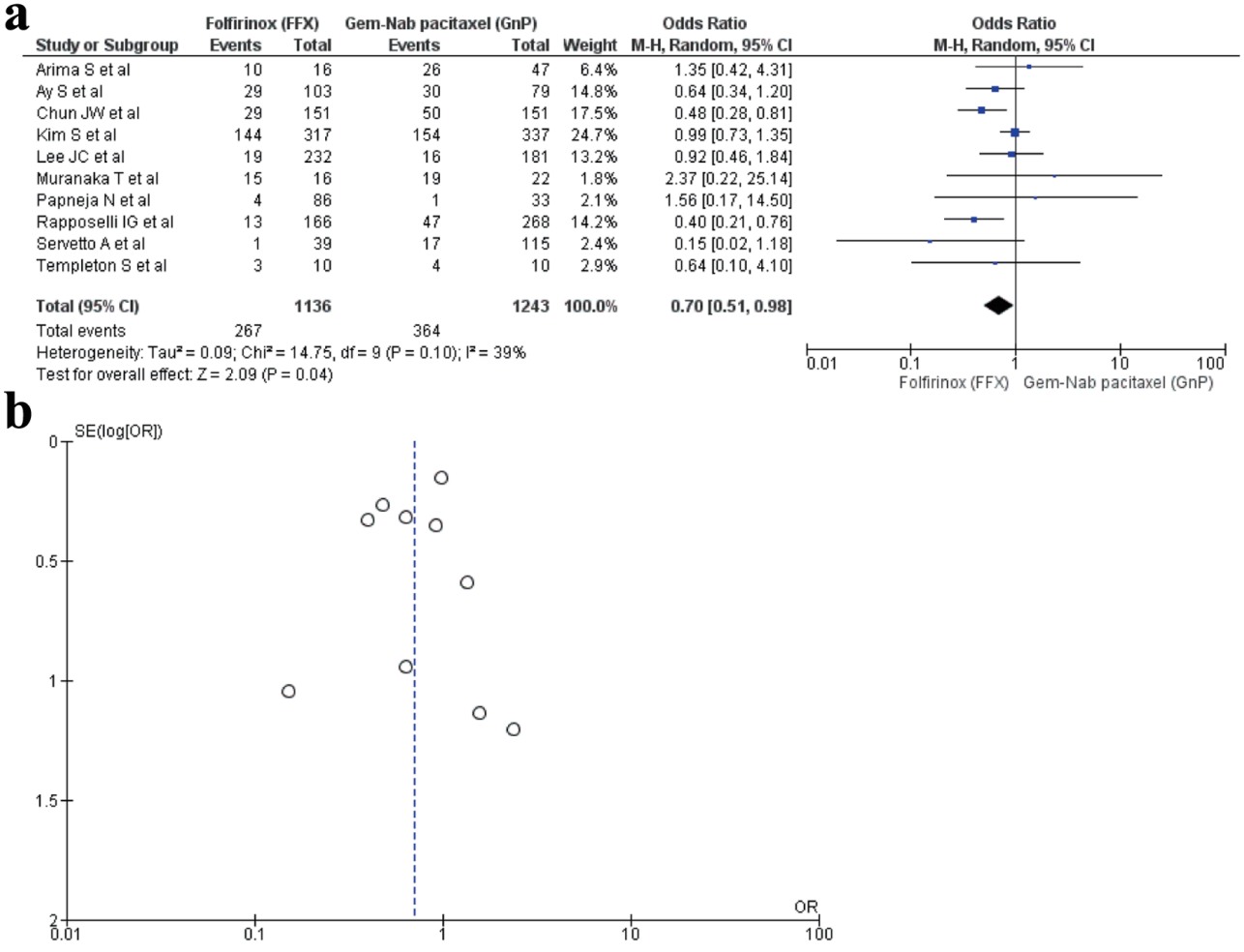
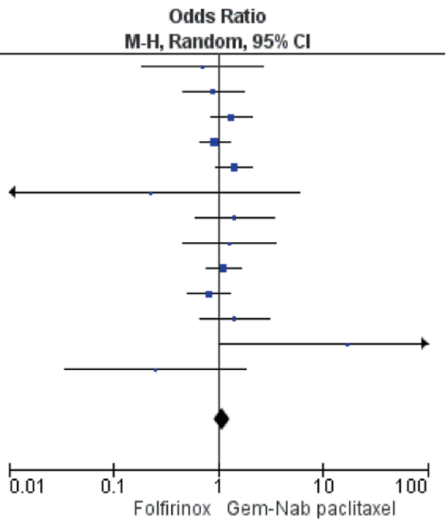


Figure 5. (a) Forest plot of anemia (OR: 0.70; 95% CI: 0.51 - 0.98; P = 0.10). (b) Funnel plot of anemia. OR: odds ratio; CI: confidence interval.

a

Study or Subgroup	Folfirinox (FFX) Events	Total	Gem-Nab pacitaxel (GnP) Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Arima S et al	12	16	38	47	1.7%	0.71 [0.19, 2.73]
Ay S et al	24	103	20	79	6.3%	0.90 [0.45, 1.77]
Chun JW et al	78	151	67	151	12.8%	1.34 [0.85, 2.11]
Kim S et al	101	317	113	337	21.0%	0.93 [0.67, 1.29]
Lee JC et al	106	232	67	181	15.8%	1.43 [0.96, 2.13]
Muranaka T et al	15	16	22	22	0.3%	0.23 [0.01, 6.01]
Nakazawa J et al	16	119	9	92	4.0%	1.43 [0.60, 3.41]
Papneja N et al	19	86	6	33	2.9%	1.28 [0.46, 3.54]
Rapposelli IG et al	75	164	115	268	16.2%	1.12 [0.76, 1.66]
Riedl JM et al	35	158	77	297	12.6%	0.81 [0.52, 1.28]
Servetto A et al	15	39	35	115	5.2%	1.43 [0.67, 3.05]
Sigel K et al	9	353	0	317	0.4%	17.51 [1.02, 302.09]
Templeton S et al	2	10	5	10	0.8%	0.25 [0.03, 1.82]
Total (95% CI)		**1764**		**1949**	**100.0%**	**1.10 [0.92, 1.31]**
Total events	507		574			

Heterogeneity: Tau² = 0.01; Chi² = 13.50, df = 12 (P = 0.33); I² = 11%
Test for overall effect: Z = 1.02 (P = 0.31)



b

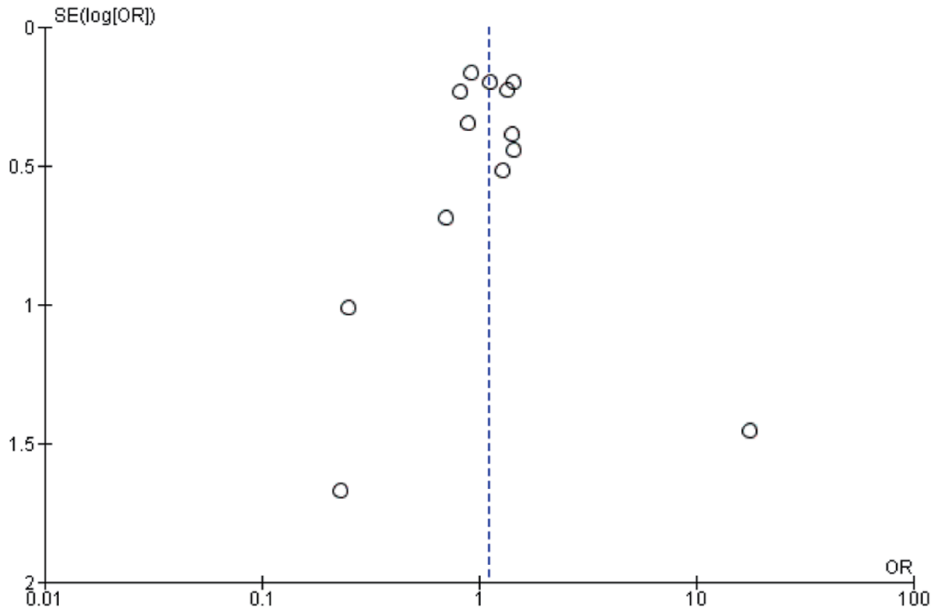


Figure 6. (a) Forest plot of neutropenia (OR: 1.10; 95% CI: 0.92 - 1.31; P = 0.33). (b) Funnel plot of neutropenia. OR: odds ratio; CI: confidence interval.

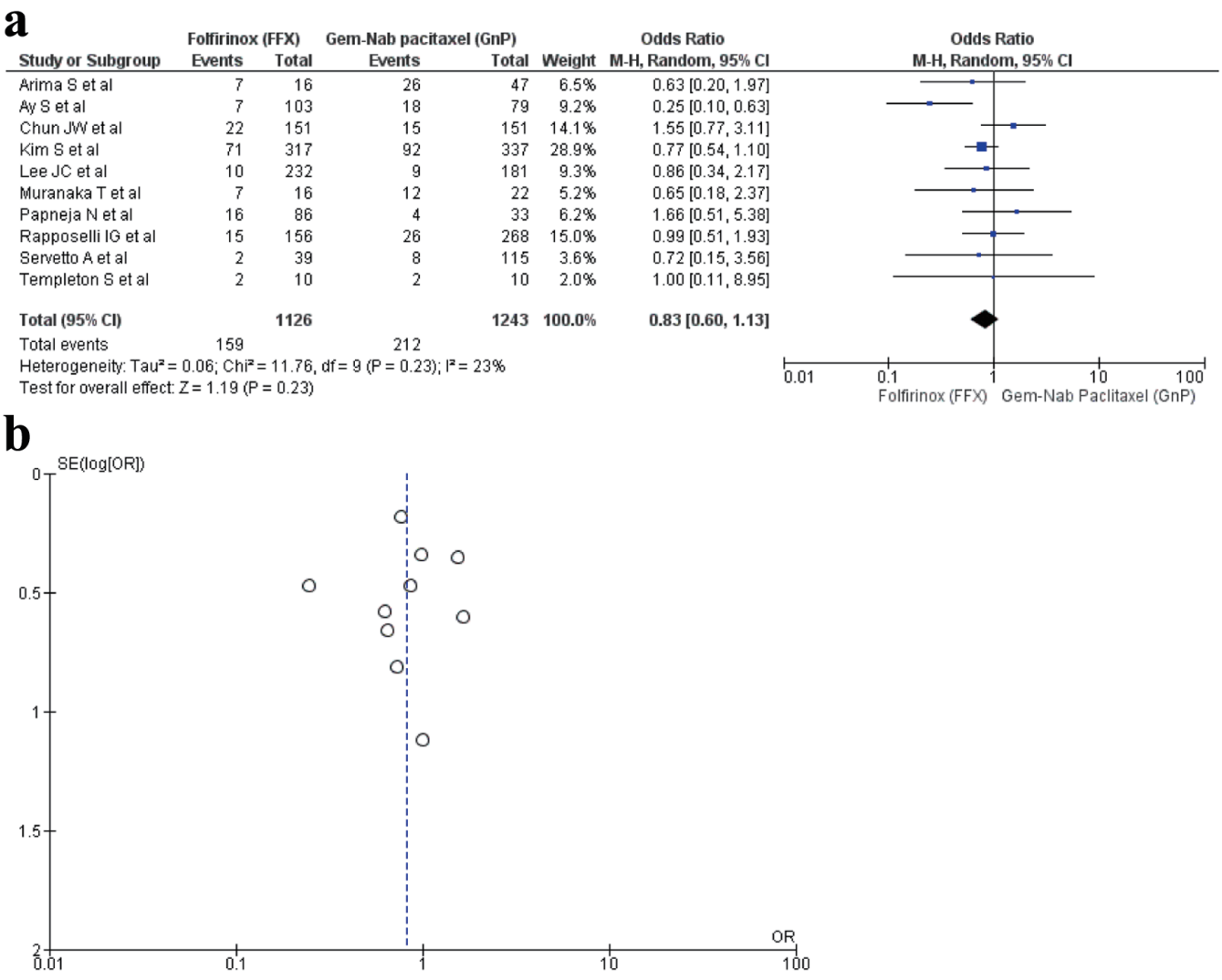


Figure 7. (a) Forest plot of thrombocytopenia (OR: 0.83; 95% CI: 0.60 - 1.13; P = 0.23). (b) Funnel plot of thrombocytopenia.

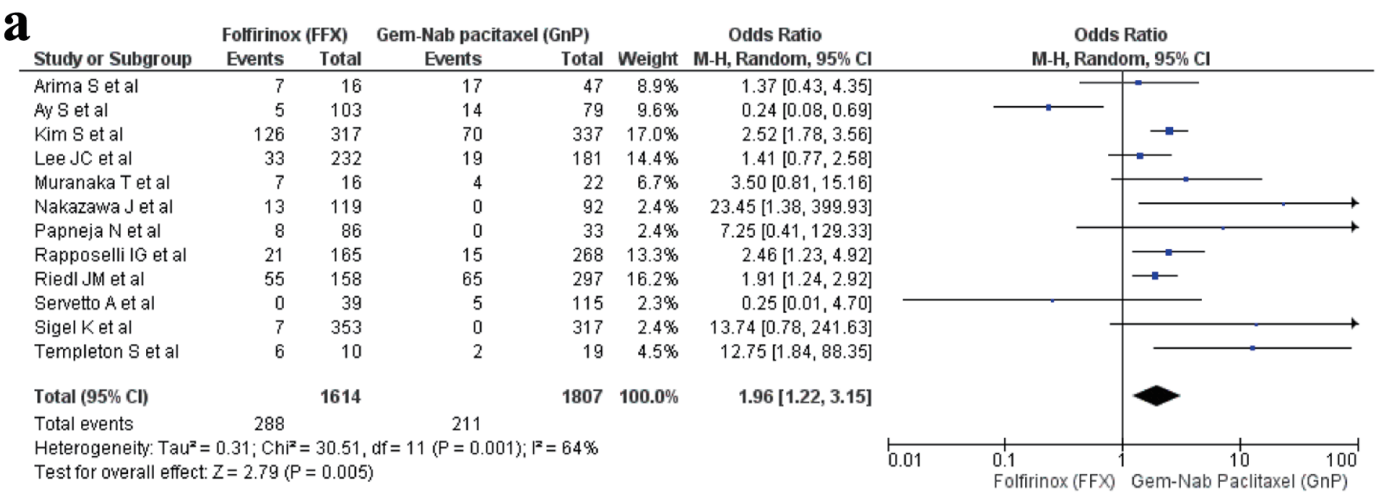


Figure 8. (a) Forest plot of diarrhea (OR: 1.96; 95% CI: 1.22 - 3.15; P = 0.001). (b) Funnel plot of diarrhea. OR: odds ratio; CI: confidence interval.

the manuscript for important intellectual content.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

FFX: Folfirinox; GnP: gemcitabine + nab-paclitaxel; HRs: hazard ratios; OR: odds ratio; ORR: objective response rate; OS: overall survival; PC: pancreatic cancer; PFS: progression-free survival

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