

The Clinical Efficacy and Safety of Paclitaxel in Adjuvant Therapy of Breast Cancer: A Systematic Review and Meta-Analysis

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Abstract: Purpose: To systematically review the clinical efficacy and adverse reactions of Paclitaxel for the treatment of mammary cancer.

Math: We searched Web of knowledge, PubMed, VIP information and CNKI (to October 2013) on randomised controlled trial about Paclitaxel for the treatment of mammary cancer and retrieved relevant reference and research material by hand. Two authors independently screened document, extracted data and assessed the quality according to inclusion and exclusion criteria, we finally used the software RevMan 5.2 from Cochrane for Meta-analysis.

Result: 18 randomized controlled clinical study were brought into our study according to inclusion and exclusion criteria, including 10712 patients. The result of meta-analysis showed that the odds ratios of Paclitaxel for adjunctive therapy [OR = 1.64, 95% CI (1.40, 1.92), P < 0.00001] was better than conventional drugs, while the overall survival was no significant difference between Paclitaxel and conventional drugs. The further Subgroup analysis showed that the efficacy of Paclitaxel for adjunctive therapy was better than cyclophosphamide [OR = 1.41, 95%CI (1.07, 1.85), P = 0.01] and NVB [OR = 2.10, 95% CI (1.33, 3.30), P = 0.001]. The adverse reactions analysis results showed the ratio of myelosuppression and alopecia by treated with Paclitaxel was improved, while the occurrence of gastrointestinal reaction rate was decreased.

Conclusion: The current evidence showed Paclitaxel was effective for the adjuvant treatment of breast cancer, but the above conclusions still need future expansion of more samples, high quality RCT verify.

Keyword: Paclitaxel, Breast cancer, efficacy, adverse reactions, systematically review, Meta-analysis, randomized controlled trial.

INTRODUCTION

Breast cancer is the world's highest incidence of malignant tumor, and also the leading cause of female death. In 2008, about 1.4 million new cases of breast cancer cases occurred among worldwide, accounting for 23% of the total number of malignant tumors and 14% of cancer deaths. The global incidence of breast cancer is rising at an annual rate of 0.5%. In China, however, growth rate of breast cancer is as high as 3%-4%, which is six to eight times of the global growth rate [1]. In the past, a high rates of breast cancer was observed in females at 40-60 years of age in China, but recently the prevalence in the age younger than 40 is increasing dramatically, revealing a trend of onset at young age [2]. Obviously, breast cancer has become one of the greatest threats to woman's physical or mental health in China.

Paclitaxel, discovered from the bark of the Pacific yew (*Taxus brevifolia*) in 1963, belongs to the taxane family and is a plant-based anti-cancer agent. And it can promote the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization, resulting in the inhibition of normal breakdown of microtubules during cell division [3]. Studies have shown that taxane is effective for breast cancer. In 1994, UFDA approved paclitaxel for the treatment of recurrence and metastasis of breast cancer, and then approved for adjuvant therapy of early postoperative breast cancer after six years. However, there is currently lack of evidence-based research data for efficacy and adverse reactions of paclitaxel in adjuvant treatment of breast cancer. Therefore, this study uses the methods of meta-analysis recommended by the Cochrane Collaboration to evaluate efficacy and safety of paclitaxel in adjuvant treatment of breast cancer, with a view to understanding of paclitaxel in clinical efficacy of adjuvant treatment for breast cancer and its safety, and further rationalization of the dosing regimen, and provides references for clinical breast cancer treatment.

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1. METHODS

1.1. Data Sources and Searches

Randomized controlled trials (RCTs) in English-language of paclitaxel for the treatment of breast cancer were search through MEDLINE (until 2014.12) and the Cochrane Central Register of Controlled Trials for, and RCTs in Chinese-language were searched through CNKI (1994-2014) and CQVIP. The search strategy was shown as following: ("Paclitaxel" OR "Taxol") AND ("Breast Cancer" OR "Breast Carcinoma" OR "Breast Tumor") AND ("Clinical treatment" OR "Clinical Trial").

1.2. Inclusion Criteria

1.2.1. Type of Included Studies

Randomized controlled trials, either blinding or not.

1.2.2. Included Object

Patients with metastatic and recurrent breast cancer confirmed by pathology or cytology; patients with anthracycline-resistant advanced breast cancer; patients with postoperative recurrence and metastasis of breast cancer; patients with advanced breast cancer previously untreated; patients with operable breast cancer; patients with lymphoma-positive breast cancer.

1.2.3. Interventions

Control groups received conventional chemotherapy, and experimental groups had adjuvant treatment with paclitaxel.

1.2.4. Outcome

1.2.4.1. Criterion for Efficacy

Evaluation of clinical efficacy was in accordance with criteria set by WHO in 1979 or International Union Against Cancer Classification, including complete remission (CR), partial responses (PR), no change (NC) and development (PD). Efficiency was deemed to be CR and PR. And also one year survival rate was utilized to assess the efficacy.

1.2.4.2. Adverse Reactions

Chemotherapy side effects include nausea, vomiting, diarrhea, hair loss, leukopenia, thrombocytopenia, anemia, liver dysfunction, and cardiac toxicity, neurotoxicity, and so on. These were used to appraise safety of interventions.

1.3. Exclusion Criteria

Studies conformed to any of the following standards would be excluded: (1) does not meet the inclusion criteria; (2) experimental group treated with docetaxel; (3) the outcome described unclearly; (4) descriptive studies, non-controlled trials or animal experiments; (5) experimental group with monotherapy of paclitaxel.

1.4. Data Extraction

Two reviewers independently screened the title and abstract according to the inclusion criteria. The full texts of relevant articles were reviewed carefully. Two reviewers cross checked the included study. Any discrepancies were resolved by referencing to the third reviewer. Data from the original articles were extracted including title, authors, age, gender, diagnosis, dosage and duration of treatment, efficacy and adverse reactions.

1.5. Statistical Analysis

In current study, the heterogeneity was analyzed by using RevMan (version 5.2). When $P > 0.05$, $I^2 < 50\%$, the fixed effects model was applied to meta-analysis; when $P < 0.05$, $I^2 > 50\%$, potential factors of heterogeneity between studies were explored, such as the design scheme, measuring method, the dosage and regimen and so on. Subgroup analysis would be available for the heterogeneity caused by those factors. Random effects model would be utilized in the case that results from several similar researches generate statistical heterogeneity. Funnel chart was used to evaluate potential bias of the studies, and subgroup analysis was carried out based on different chemotherapy.

2. RESULTS

2.1. Search Results

Through the search strategy, 1544 relative studies were identified including 552 articles in Chinese and 922 articles in English. According to inclusion and exclusion criteria and restricting article type to RCT, a total of 18 studies were selected.

As shown in Table 1, 18 studies (5 Chinese articles and 13 English articles) were RCTs, but most of these articles did not specifically describe whether to adopt allocation concealment and blinding. Among them, 12 studies displayed the outcomes including the total effective rate, and 4 studies showed one year survival

Table 1: General Information of Included Studies

Included studies	Year	N		Tumor types	Intervention		Quality assessment			Outcome			
		Exp.	Con.		Exp.	Con.	Random method	Allocation concealment	Blinding	total effective rate	one year survival rate	total effective rate	one year survival rate
Liu Junli [4]	2007	26	25	Recurrent metastatic breast cancer	TP	NP	Not mentioned	Not mentioned	Not mentioned	50	59.1	40	45
Huang Fuxi [5]	2008	30	30	Recurrent metastatic breast cancer	TP	NP	Not mentioned	Not mentioned	Not mentioned	50	56.7	46.7	43.3
Huang Ximei [6]	2007	38	39	Recurrent metastatic breast cancer	TP	NP	Simple randomized	Not mentioned	Not mentioned	68.42		46.15	
Fang Shengxiang [7]	2005	58	62	Advanced breast cancer	TE	NE	Block randomized	Not mentioned	Not mentioned	65.5		38.7	
He Xinbin [8]	2010	22	19	Recurrent breast cancer	TP	GP	Not mentioned	Not mentioned	Not mentioned	45.45	59.09	47.37	57.89
Istvan Lang [9]	2013	285	279	HER2-negative metastatic breast cancer	T+BEV	CAP+ BEV	Computer random grouping	Not mentioned	Non blinding	44	81	27	79
Aman U. Buzdar [10]	2002	265	259	invasive breast cancer	FAC+T	FAC	Not mentioned	Not mentioned	Not mentioned				
Gary H. Lyman [11]	2004	45	46	Invasive breast cancer	AT	AC	Not mentioned	Not mentioned	Not mentioned	31		39	
Binghe Xu [12]	2011	49	98	Invasive breast cancer	GT	G+CBP GD+P	Not mentioned	Not mentioned	Non blinding	26.5		17.0 15.7	
Miguel Martin [13]	2010	614	632	Early-stage breast cancer	FEC+T	FEC	Not mentioned	Not mentioned	Not mentioned				
Ruth E. Langley [14]	2005	353	352	Metastatic breast cancer	ET	EC	Not mentioned	Not mentioned	Not mentioned	65		55	
I. Lang [15]	2012	284	277	HER2-negative locally recurrent or metastatic breast cancer	T+ BEV	CAP+BEV	Not mentioned	Not mentioned	Non blinding				
Miguel Martin [16]	2008	614	632	Early-stage breast cancer	FEC+T	FEC	Not mentioned	Not mentioned	Not mentioned				
Eleftherios Mamounas [17]	2005	1531	1529	Lymphoma-positive breast cancer	AC+T	AC	Not mentioned	Not mentioned	Not mentioned				
Jacek Jassem [18]	2001	134	133	Metastatic breast cancer	AT	FAC	Not mentioned	Not mentioned	Not mentioned	68		55	
George Sledge [19]	2003	230	224	Metastatic breast cancer	AT	A	Not mentioned	Not mentioned	Not mentioned	36		47	
Aman Buzdar [20]	1999	87	87	Operable breast cancer	FAC+T	FAC	Not mentioned	Not mentioned	Not mentioned	80		79	
Luca Gianni [21]	2005	880	444	Metastatic breast cancer	AT+CMF	A+CMF	Not mentioned	Not mentioned	Not mentioned				

Note: T: paclitaxel; N: navelbine; P: cisplatin; E: epirubicin; A: adriamycin; G: gemcitabine; C: cyclophosphamide; F: fluorouracil; BEV: bevacizumab; CAP: capecitabine; CBP: carboplatin; M: methotrexate.

Table 2: Information of Adverse Reactions

Included studies	Granulocytopenia		Leukocytopenia		Thrombocytopenia		Alopecia		Anemia		Diarrhea		Liver damage		Nausea		Vomiting		Nausea and vomiting	
	Exp.	Con.	Exp.	Con.	Exp.	Con.	Exp.	Con.	Exp.	Con.	Exp.	Con.	Exp.	Con.	Exp.	Con.	Exp.	Con.	Exp.	Con.
Liu Junli	15/26	12/25			5/26	4/25													14/26	12/25
Huang Fuxi	16/30	15/30			6/30	5/30													16/30	15/30
Huang Ximei			22/38	24/39			30/38	29/39			4/38	5/39	9/38	10/39					16/38	19/39
Fang Shengxiang			33/58	38/62	15/58	10/62	51/58	48/62	20/58	19/62			15/58	17/62					27/58	33/62
He Xinbin	13/22	11/19			7/22	7/19													14/22	11/19
Istvan Lang	85/284	13/277	45/284	6/277			86/284	5/277	33/284	20/277	55/284	60/277			56/284	66/277	28/284	33/277		
Aman U. Buzdar	44/265	24/259																		
Gary H. Lyman	34/45	31/46	31/45	32/46	6/45	4/46			9/45	9/46	1/45	1/46			2/45	6/46	2/45	5/46		
Binghe Xu	16/49	19/97	7/49	8/97	2/49	4/97	1/49	1/97	3/49	9/97			0/49	1/97	0/49	8/97	0/49	9/97		
Ruth E. Langley							238/334	204/331											33/334	42/331
I. Lang	72/284	11/277	39/284	5/277			75/284	4/277	30/284	17/277	49/284	57/277			49/284	56/277	26/284	28/277		
Miguel Martin	117/614	161/632													33/614	37/632	45/614	63/632		
Jacek Jassem	119/134	86/133			3/134	4/133			12/134	9/133	3/134	0/133							11/134	25/133
George W. Sledge			126/230	111/224	37/230	12/224			40/230	14/224	10/230	4/224					10/230	15/224		
Aman U. Buzdar											3/87	14/87			9/87	18/87	2/87	6/87		
Luca Gianni	15/880	10/444																		

Note: In addition to liver damage, adverse reactions were analyzed by frequency. Data of nausea, vomiting and nausea and vomiting in the studies could not be merged due to inconsistent description.

rate. Although other endpoints such as four years survival rate, five years survival rate and seven years survival rate were reported, the number was not enough for statistical analysis. Besides, the median survival, the disease-free survival and the median period of disease progression were impossibly calculated due to the lack of variance.

2.1.1. Patients and Interventions

In 18 RCTs, a total of 10712 cases diagnosed with breast cancer were included, dividing into control group (5167) and experimental group (5545). Control group applied conventional chemotherapy (epirubicin plus navelbine or navelbine plus cisplatin, etc.), while experimental group utilized adjuvant treatment with paclitaxel (paclitaxel plus cisplatin or paclitaxel plus epirubicin, etc.).

2.2. Quality Assessment Niyou

The Cochrane Collaboration's tool for assessing risk of bias in randomized trials was used to evaluate the quality of RCTs. In this study, 18 RCTs were included. Among them, three studies illustrated the specific method of randomization, while none mentioned allocation concealment. Four studies were conducted under the method of non-blinding but the rest were unclear. All of the 18 included studies showed favorable quality (see Figure 1).

2.3. Outcomes

2.3.1. Total Effective Rate

Total effective rate is one of the important indicators to determine the efficacy. Twelve included studies had reported total effective rates in patients with no

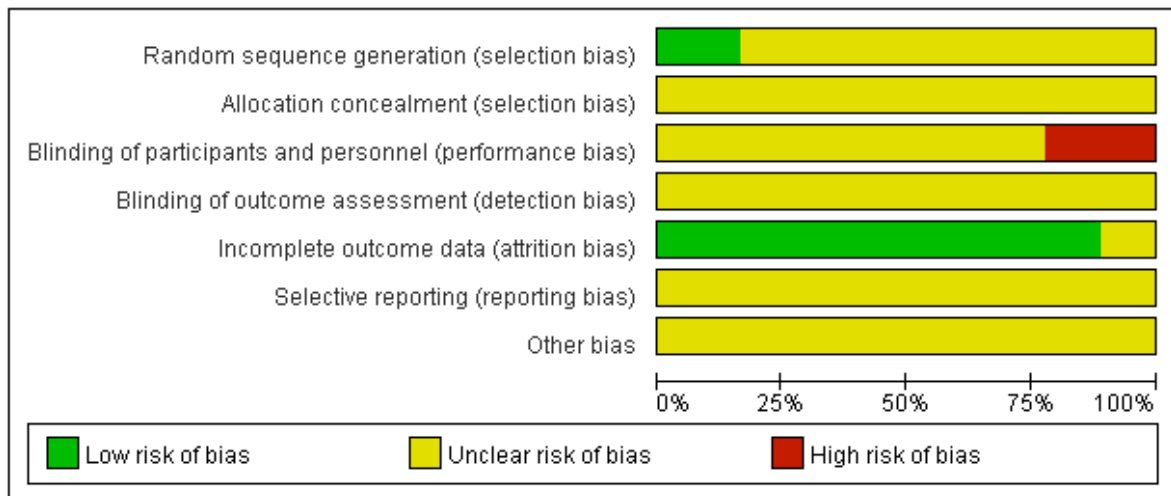


Figure 1: Quality assessment of included studies.

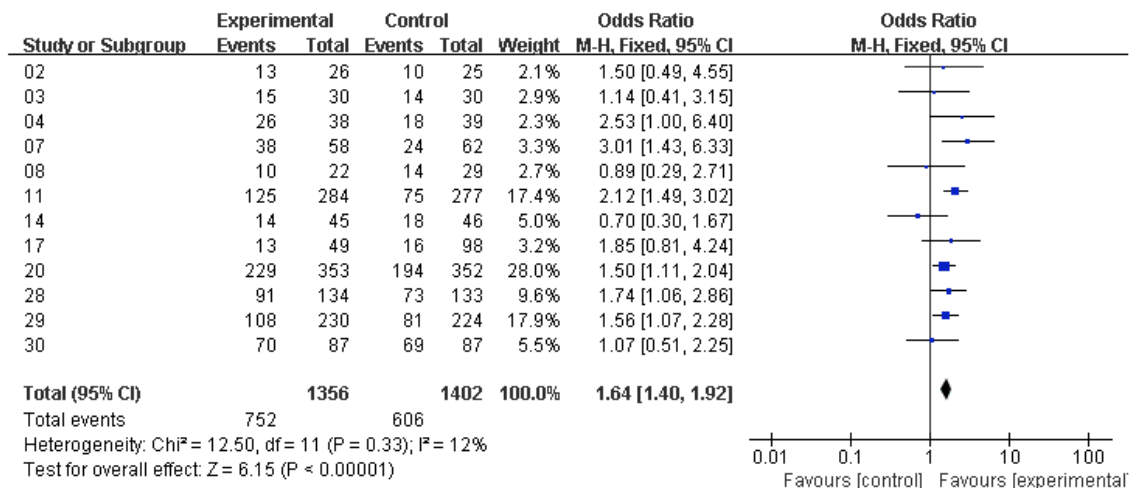


Figure 2: forest plots and meta-analysis of total effective rate.

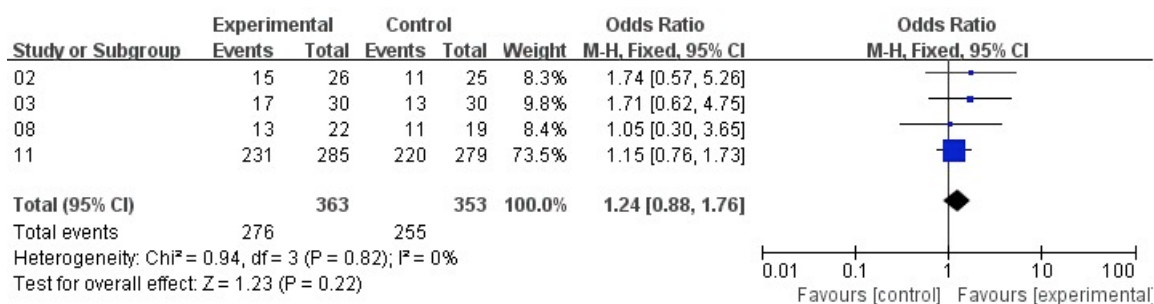


Figure 3: Forest plots and meta-analysis of one year survival rate.

heterogeneity ($\chi^2 = 12.50$; $P > 0.05$; $I^2 = 12\%$). In Figure 2, Meta-analysis results showed that the efficacy of experimental group was significantly superior to control group (OR = 1.64; 95% CI 1.40 to 1.92; $P < 0.00001$).

2.3.2. One Year Survival Rate

In 18 included studies, four of them demonstrated one year survival rate without heterogeneity ($\chi^2 = 0.94$; $P = 0.82$; $I^2 = 0\%$). In Figure 3, Meta-analysis suggested that there was no significant difference (OR=1.24; 95% CI 0.88 to 1.76; $P=0.22$).

2.3.3. Subgroup Analysis

For the total effective rate, 15 studies exhibited heterogeneity, so subgroup analysis was applied to explore it. The first subgroup analysis was for the effectiveness evaluation of navelbine combined with paclitaxel in 4 studies that showed no heterogeneity ($\chi^2 = 2.79$; $P = 0.43$; $I^2 = 0\%$). In Figure 4, Meta-analysis showed that the experimental group was significantly

better than the control group (OR = 2.10; 95% CI 1.33 to 3.33; $P = 0.001$). In the same way, the second subgroup analysis was for the effectiveness evaluation of cyclophosphamide combined with paclitaxel in 3 studies without heterogeneity ($\chi^2 = 2.86$; $P = 0.24$; $I^2 = 30\%$). Meta-analysis in Figure 4 also demonstrated that the experimental group was better than the control group (OR = 1.41; 95% CI 1.07 to 1.85; $P = 0.01$).

2.4. Adverse Reactions

2.4.1. Granulocytopenia

Eleven included studies had reported incidence of granulocytopenia while represented significant heterogeneity ($\chi^2 = 124.99$; $P < 0.05$; $I^2 = 92\%$). Thus, the random-effects model was used to analyze it. The combining data in Figure 5 showed that incidence of granulocytopenia in the experimental group was significantly higher than control group (OR 2.05; 95% CI 1.08 to 3.88; $P = 0.03$).

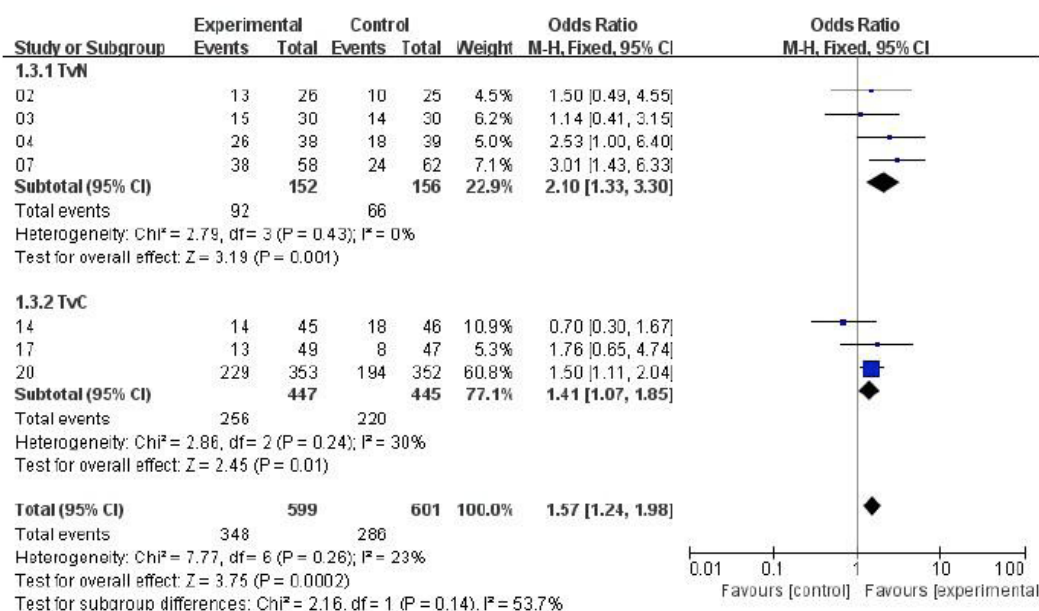


Figure 4: Forest plots and meta-analysis of subgroup analysis.

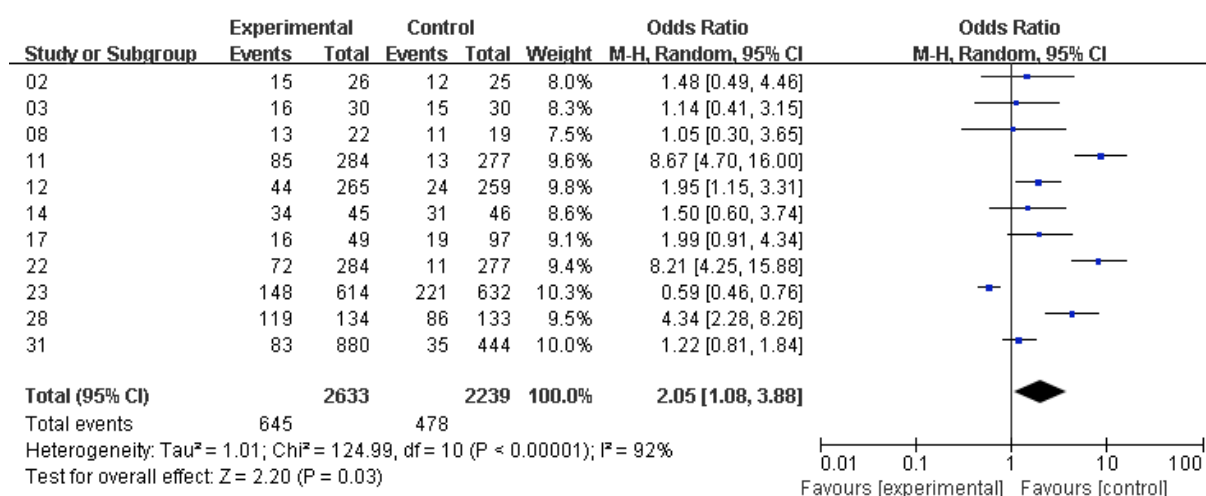


Figure 5: Forest plots and meta-analysis of incidence of granulocytopenia.

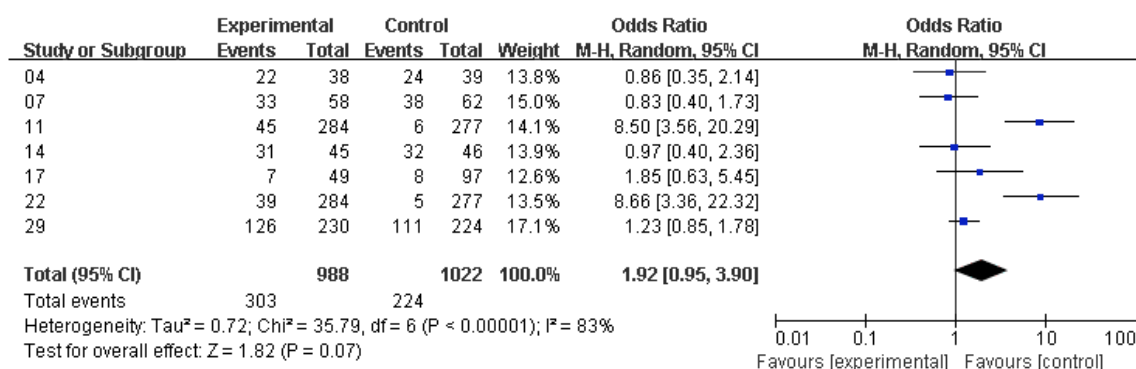


Figure 6: Forest plots and meta-analysis of incidence of leucopenia.

2.4.2. Leukopenia

In 7 included studies, compared with control group, paclitaxel group displayed nonsignificant difference in the incidence of leukopenia ($OR = 1.92$; 95% CI 0.95 to 3.90; $P = 0.07$) (Figure 6). And obvious heterogeneity was detected ($\chi^2 = 35.79$; $P < 0.05$; $I^2 = 83\%$).

2.4.3. Thrombopenia

The pooled results of 8 included studies in Figure 7 demonstrated that the experimental group was inclined to cause thrombopenia ($OR = 1.81$; 95% CI 1.23 to 2.65; $P = 0.003$). There was nonsignificant heterogeneity ($\chi^2 = 7.19$; $P = 0.41$; $I^2 = 3\% < 50\%$).

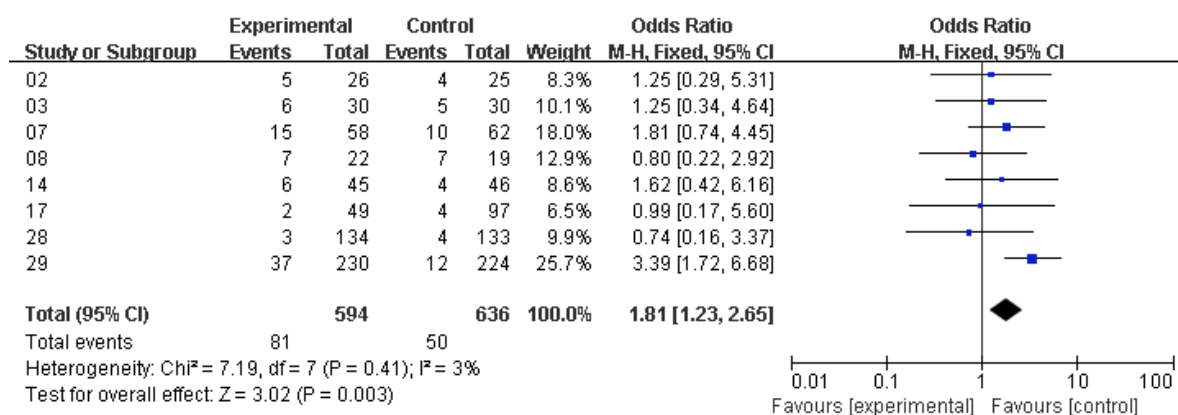


Figure 7: Forest plots and meta-analysis of incidence of thrombopenia.

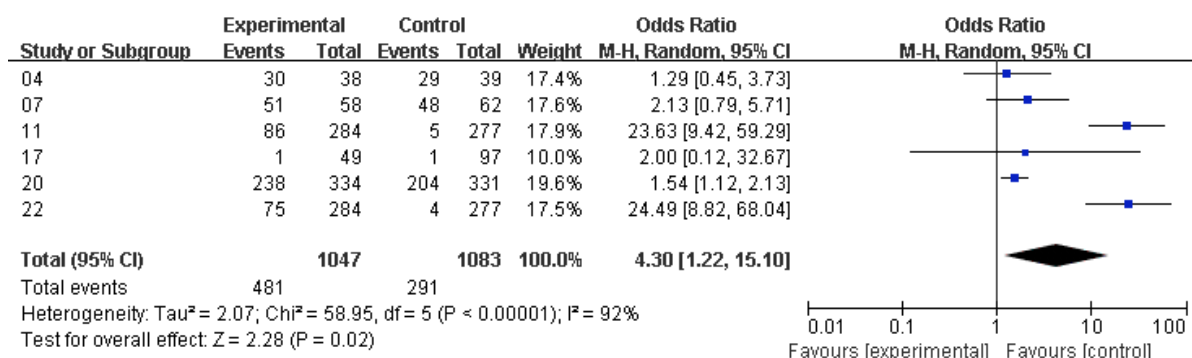


Figure 8: Forest plots and meta-analysis of the adverse reaction of hair loss.

2.4.4. Hair Loss

Six studies investigated the adverse reaction of hair loss. As there was significant heterogeneity among studies ($\chi^2 = 58.95$; $P < 0.05$; $I^2 = 92\%$), and random-effects model was carried out to assess it. The pooled data in Figure 8 indicated that incidence of hair loss was significantly higher in paclitaxel group (OR = 4.30; 95% CI 1.22 to 15.10; $P = 0.02$).

2.4.5. Anemia

Among included literatures, 6 studies reported the observation of anemia in patients without heterogeneity

($\chi^2 = 7.36$; $P = 0.27$; $I^2 = 21\%$). By using fixed-effects model, the combined data in Figure 9 implied that adjuvant therapy with paclitaxel more likely increased the incidence of anemia (OR = 1.68; 95% CI 1.28 to 2.28; $P = 0.0002$).

2.4.6. Diarrhea

Seven studies observed the incidence of diarrhea during treatment. The pooled data in Figure 10 revealed no significant difference (OR = 0.84; 95% CI 0.65 to 1.10; $P = 0.2$; $I^2 = 44\%$).

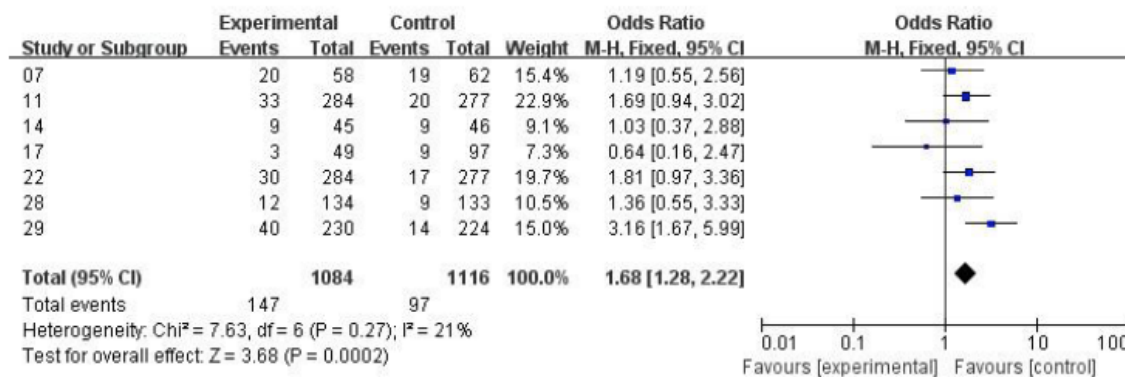


Figure 9: Forest plots and meta-analysis of anemia.

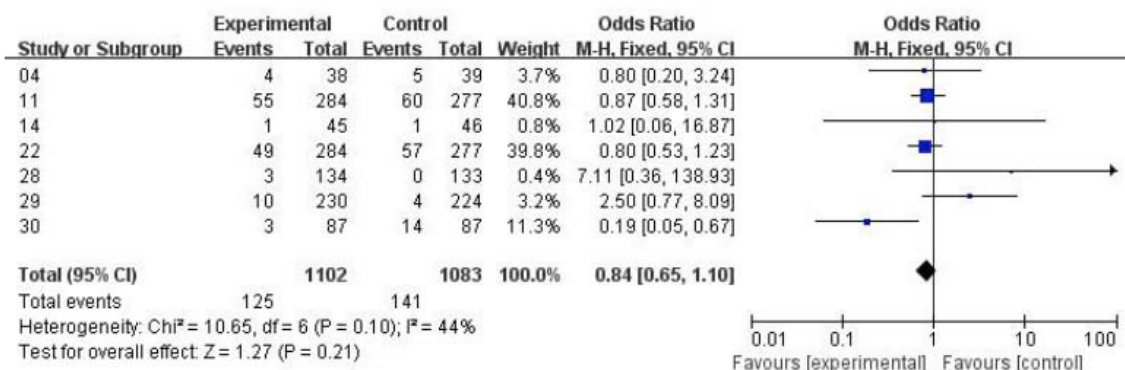


Figure 10: Forest plots and meta-analysis of incidence of diarrhea.

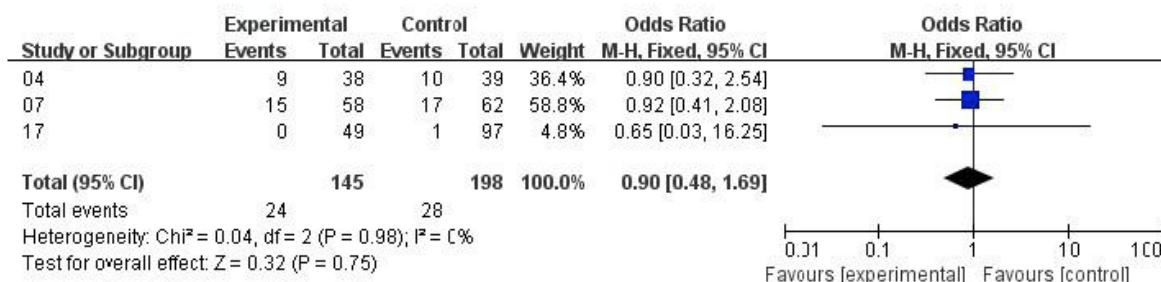


Figure 11: Forest plots and meta-analysis of hepatotoxicity.

2.4.7. Hepatotoxicity

Hepatotoxicity of paclitaxel was evaluated in three trials among which had no heterogeneity ($\chi^2 = 0.04$; $P = 0.98$; $I^2 = 0\%$). As the pooled result showed in Figure 11, paclitaxel may be not associated with liver damage (OR = 0.90; 95% CI 0.48 to 1.69; $P = 0.75$).

2.4.8. Nausea and Vomiting

Nausea and vomiting was observed in 7 studies that showed nonsignificant heterogeneity ($\chi^2 = 5.18$; $P = 0.52$; $I^2 = 0\%$). In Figure 12, Meta-analysis indicated that the incidence of nausea and vomiting was lower in paclitaxel group than control group (OR = 0.75; 95% CI 0.56 to 1.00; $P = 0.05$).

2.4.9. Nausea

Six studies investigated the incidence of nausea in patients without significant heterogeneity ($\chi^2 = 5.18$; $P = 0.39$; $I^2 = 3\%$). The pooled data in Figure 13 indicated that paclitaxel adjunctive therapy likely decreased the incidence of nausea compared with experimental group (OR = 0.75; 95% CI 0.59 to 1.00; $P = 0.02$).

2.4.10. Vomiting

Seven literatures discussed the incidence of vomiting, and no heterogeneity was detected among them ($\chi^2 = 4.35$; $P > 4.35$; $I^2 = 0\%$). In Figure 14, Meta-analysis of pooled results demonstrated that the incidence of vomiting were lower to be observed in

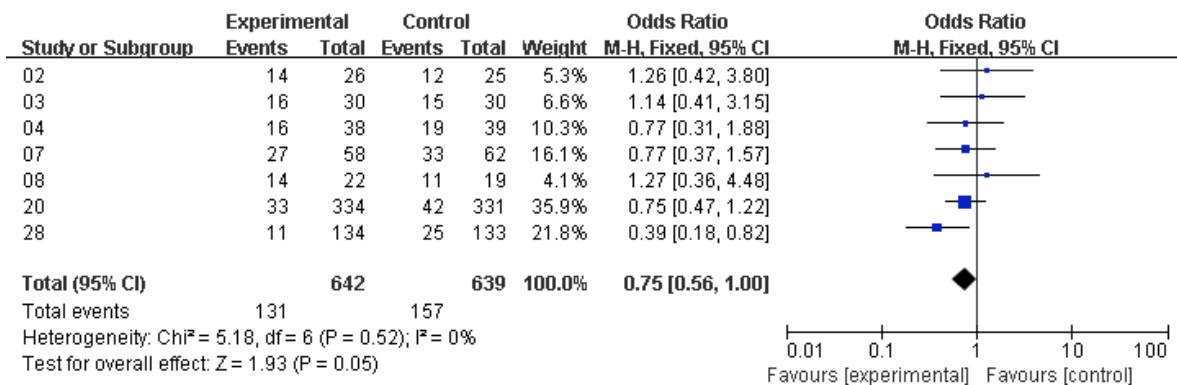


Figure 12: Forest plots and meta-analysis of nausea and vomiting.

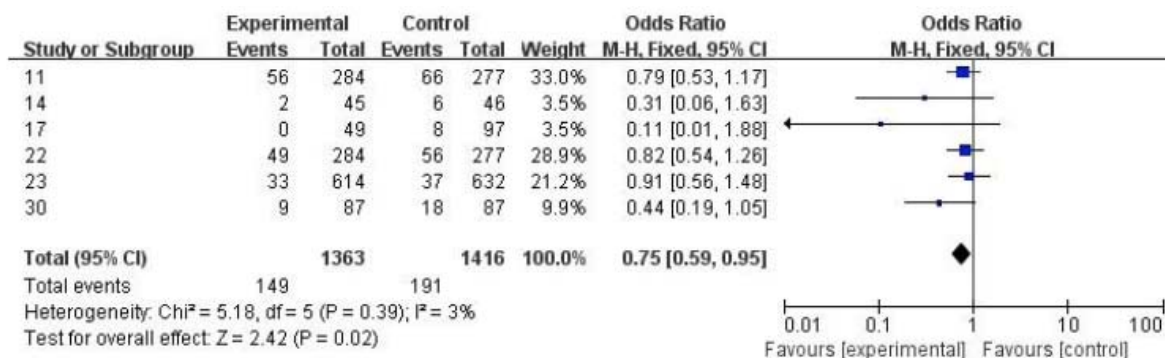


Figure 13: Forest plots and meta-analysis of the incidence of nausea.

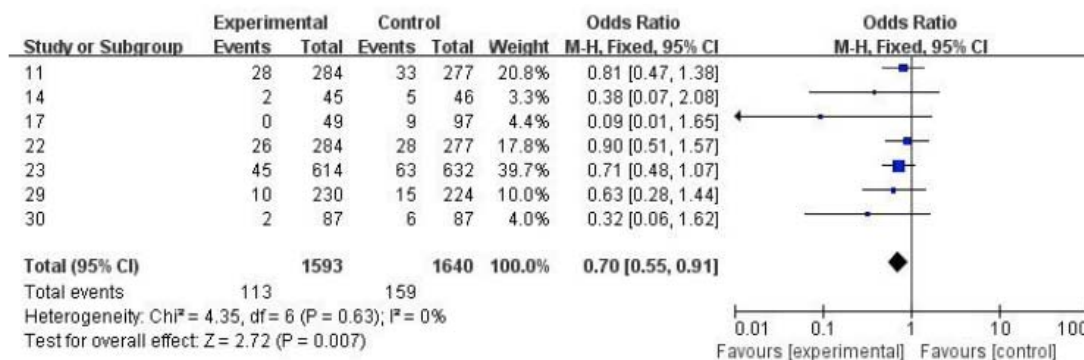


Figure 14: Forest plots and meta-analysis of the incidence of vomiting.

paclitaxel group than control group (OR = 0.70; 95% CI 0.55 to 0.91; P = 0.007).

3. DISCUSSION

In this current study, we aim to objectively evaluate the efficacy and safety of paclitaxel in the adjuvant treatment of breast cancer through the method of evidence-based medicine in order to provide reasonable evidence for clinical cancer therapy.

Through the process of literature search, 18 RCTs met the inclusion criterion were eventually included. These trials revealed that paclitaxel adjuvant therapy for breast cancer exhibits certain efficacy. In aspect of anticancer efficacy, the pooled results suggest that adjuvant therapy with paclitaxel displays superior efficacy to breast cancer compared with common treatment, whereas there was no significant difference in one year survival rate between paclitaxel groups and control groups. With regard to drug safety, paclitaxel may tend to increase the incidences of granulocytopenia, thrombopenia, hair loss and anemia, which are commonly to be observed in clinical practice. In contrast, meta-analysis implies that paclitaxel adjunct therapy may help to reduce adverse reactions including nausea or vomiting. In current study, there was significant heterogeneity among the 12 included trials that reported the total effective rate. In order to deeply elaborate, we further conducted a subgroup analysis of total effective rate. The pooled result suggests that, adjunct therapy with paclitaxel may achieve a better total effective rate compared with navelbine and cyclophosphamide. Also, our study reaches a conclusion that paclitaxel as an adjuvant antitumor drug can produce favorable efficacy for breast cancer therapy, and provides reliable information about the safety and toxicity of paclitaxel, which will be beneficial to clinical decision-making and rationalized regimen for breast cancer treatment.

Indeed, our current study also has certain limitations. Firstly, we were unable to include high-quality RCT, which is well designed and strictly conducted under randomization and double-blinding. Among 18 included trials, three were performed under non-blinding method, while the rest failed to mention it. All of them did not refer to allocation concealment, and only three offered the specific of randomization method while others just mentioned in randomization without any detail. To some extent, those limitations would affect the pooled result of the comparison between experimental group and control group. Secondly, our current study showed that, funnel plots appear to be asymmetric and display skewness distribution, revealing the publishing bias that negative result may not be published. In most cases, factors contributing to published bias contain statistical significance of treatment effect, sample size, treatment innovativeness, importance of research, quality of trial, research fund and so on [22].

In addition, the pooled result implies that paclitaxel adjuvant therapy can achieve better efficacy. In these 18 included studies, however, the therapeutic drugs combined with paclitaxel were diverse, resulting in production of bias. And still, further clinical trials demand to be performed to evaluate the cost-benefit of paclitaxel in the treatment of breast cancer.

To sum up, adjunct therapy with paclitaxel may show certain efficacy on breast cancer despite resulting in some types of adverse reactions. However, this current study inevitably has some inherent limitations due to the quality of included trials. Future large-volume, well-designed RCTs are still demanded to deeply explore the efficacy and safety of paclitaxel adjunct therapy for breast cancer.

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