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Effects of different targeted therapies associated with adjuvant chemotherapy on clinical remission, survival and safety in patients with triple-negative breast cancer: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: The aim of this study was to systematically assess the effects of different targeted therapies associated with adjuvant chemotherapy on clinical remission, survival and safety of patients with triple-negative breast cancer (TNBC).

MATERIALS AND METHODS: This study searched for case-control trials of TNBC patients from January 2010 to May 2022. Two researchers independently extracted data. RevMan 5.3 statistical software was used for analysis.

RESULTS: This study included a total of 7 clinical controlled studies, containing 620 samples. The results showed that compared with the control group, the study group showed significant differences in objective response rate [OR = 2.44, 95% CI (1.69, 3.5), $p < 0.00001$], 1-year survival rate [OR = 3.59, 95% CI (2.01, 6.39), $p < 0.0001$], progression-free survival (PFS) [MD = 2.04, 95% CI (1.68, 2.41), $p < 0.00001$], with statistical significance ($p < 0.05$), while there are no significant differences in overall survival [MD = 6.33, 95% CI (-1.65, 14.30), $p = 0.12$] and incidence of adverse events [OR = 0.73, 95% CI (0.52, 1.02), $p = 0.006$] ($p > 0.05$).

CONCLUSIONS: Targeted therapy associated with adjuvant chemotherapy can remarkably enhance the outcome of patients with advanced TNBC, prolonging their progression-free survival (PFS) and overall survival (OS) without increasing adverse effects. The validity of this research, however, will require higher quality studies and longer follow-ups.

Key Words:
Targeted therapy, Adjuvant chemotherapy, Triple-negative breast cancer, Adverse event of special interest.

Introduction

In terms of the number of cases in women, breast cancer ranks second in the world. Many measures, including early detection and effective treatment, have contributed to a dramatic drop in breast cancer mortality rates over the last three decades[1]. There are many biological characteristics and clinical manifestations associated with breast cancer, which makes it a type of solid tumor. Many clinical and pathological features have been used to predict efficacy and prognosis, including age, tumor size, axillary lymph node involvement, vascular lymphatic invasion, histologically graded estrogen receptor (ER) status, progesterone receptor (PR) status and human epidermal growth factor receptor-2 (*HER-2*) gene expression[2]. Breast cancer cells do not express these three receptors, so they are referred to as triple-negative breast cancer (TNBC) cells[3].

Statistics[4] shows that TNBC accounts for between 10.4% and 16.3% of all breast cancers. However, the incidence rate in Americans is as high as 20.8%, including early menarche and full-term pregnancy age, short lactation period, and breast cancer susceptibility gene 1 (*BRCA1*) mutation carriers, especially in premenopausal patients. The proportion of TNBC with histological grade III was higher compared to non-TNBC (64.8% *vs.* 25.6%), and the average diameter of the primary tumor was larger (3.1 cm *vs.* 2.0 cm). The positive rate of lymph nodes was slightly higher compared to non-TNBC (53.6% *vs.* 46.8%)5. For patients with non-TNBC, the rate of positive lymph nodes detected correlates positively with

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tumor diameter. Previous studies[6] have shown that the positive rate of lymph nodes in patients with tumors < 1 cm is 55%, while the corresponding proportion is only 19%.

It takes about 1-3 years after surgery for TNBC to recur locally and metastasize distantly, and then the risk gradually declines[7]. Metastatic patterns in TNBC differ from those in non-TNBC. The TNBC pattern is more common in visceral and soft tissue metastases, such as brain, liver, lung, spinal cord, and meninges, while bone metastases are less obvious. The overall survival (OS) of TNBC after recurrence and metastasis was shorter, and 70% of the deaths occurred within 5 years after diagnosis, compared with 44% of non-TNBC[8].

At present, there is no specific treatment guideline for TNBC and its related standard treatment plan. Treatment options for TNBC are limited, so most patients are limited to anthracyclines, paclitaxel, and cyclophosphamide[9,10]. Various studies have shown them to be highly chemo-sensitive to these tumor cells, sometimes even achieving complete pathological responses (CPR). Even with neoadjuvant chemotherapy, disease-free survival (DFS) and overall survival rates for TNBC patients remain lower than those for non-TNBC[11]. TNBC shows heterogeneity in chemotherapy response, and in a clinical trial[12] testing the implications of neoadjuvant chemotherapy, the CPR increased from 12% for monotherapy to 27%-65% for multi-drug therapy.

Targeted therapy for TNBC has been applied clinically, mainly including poly ADP-ribose polymerase (PARP) inhibitors, anti-Trop-2 antibody conjugates, antibody-drug conjugates (ADC), androgen receptor (AR) antagonists and anti-angiogenic drugs[13,14]. Several studies[15-17] evaluated targeted therapy combined with adjuvant chemotherapy, indicating that this combination is highly valuable in clinical treatment. There are significant differences in research designs, evaluation indicators, and conclusions. Therefore, more authoritative scientific research is needed to demonstrate the therapeutic effect of targeted therapy combined with adjuvant chemotherapy on TNBC patients to provide a theoretical basis for the promotion and application of this treatment. This study conducted a meta-analysis of similar independent studies to evaluate the effects of different targeted therapies combined with adjuvant chemotherapy on the clinical remission, survival and safety of TNBC patients.

Materials and Methods

The Sources and Retrieval Methods of Documents

PubMed, EMBASE, ScienceDirect, Cochrane Library, China Journal full-text Database (CNKI), VIP full-text Database, Wanfang Database and Chinese Biomedical Literature data (CBM), as well as relevant Chinese and foreign periodicals, conference papers, degree papers, supplemented by literature tracing, were searched. The control group included patients with TNBC receiving targeted therapy and adjuvant chemotherapy. A literature search was conducted with free words plus subject words, with the keywords of targeted therapy, adjuvant chemotherapy, TNBC, clinical remission, survival, safety evaluation, meta-analysis, targeted therapy; from January 2010 to May 2022.

Literature Inclusion and Exclusion Criteria

Literature inclusion criteria

(1) The type of study: case-control studies of targeted therapy in patients with TNBC in conjunction with adjuvant chemotherapy. (2) Subjects: TNBC was diagnosed by clinical pathology and imaging examination, the diagnostic criteria were referred to relevant literature[18], the score of Karnofsky functional status (KPS)[19] was $\geq$ 40, the expected survival time was $\geq$ 3 months, and the results of blood routine, liver and kidney function tests were normal. (3) Intervention: the study group was cured with targeted therapy associated with adjuvant chemotherapy, while the control group only accepted targeted therapy or adjuvant chemotherapy. Targeted therapy was indicated for patients with *HER-2* positive, while adjuvant chemotherapy was indicated for patients with local complete breast cancer (TNM stage II or III); breast cancer with large mass or axillary lymph node metastasis; early invasive breast cancer patients whose primary tumor was large and difficult to perform breast-conserving surgery, but patients with breast-conserving desire; breast cancer patients who needed further operation because of non-standard operation after radical operation. Adverse events (AE) were graded according to the previous standards[14].

Literature exclusion standard

(1) No cases and controls; (2) it was not possible to use the data since the report was incomplete; (3) research content replicates; (4) study results were not remarkable in terms of curative effects; (5) review of related literature; (6) clinical cases.

Quality Evaluation and Data Extraction

This study followed the current guidelines of PRISMA. 1) For assessing bias risk, Cochrane System Review Manual 5.3[20] was adopted, which is recommended by the Cochrane system. 2) Literature screening and data extraction: there were two independent screenings of the literature conducted by two researchers. A third researcher would be asked to assist with the judgment in case of differences in the quality of the data. A document management software program called Note Express and an office software package called Excel were adopted to manage and extract research data. In the event that the literature contained incomplete data, the author of this article can be contacted to complete the information. The contents of data extraction include (1) basic information: author, publication time, number of cases; (2) intervention measures: scheme, course of treatment; (3) outcome indicators: objective remission rate, 1-year survival rate, total survival time, PFS time and incidence of AEs.

Statistical Analysis

For the meta-analysis, RevMan 5.3 (The Cochrane Centre, Oxford, UK) software was used. Counting data was analyzed using relative risk (OR), and measurement data were analyzed using mean difference (MD). We gave the point estimate and 95% confidence interval (CI) for each effect quantity. For heterogeneity, we used the χ^2 test, and we judged heterogeneity using I^2. Fixed effect models are adopted if there is no heterogeneity; if there is heterogeneity, subgroup, sensitivity, or descriptive analyses are adopted, and the random effect model is adopted if there is heterogeneity. $p < 0.05$ was statistically remarkable. Further analysis of the literature's publication bias was conducted using an inverted funnel chart. Eggers's test was used to check the asymmetry of the funnel chart. Whenever the p-value of this test was less than 0.1, the Trim and Fill method could be used to correct the funnel chart and adjust the effect of the potential release deviation.

Results

Results of Literature Retrieval and Literature Inclusion

We used a computer database to retrieve 1,562 articles, 893 articles were eliminated after removing repeated studies and 416 were retrieved by reading the titles and abstracts. After excluding irrelevant studies, reviews, case reports, and non-control literature, 188 articles were obtained, of which 181 had incomplete data and failed to highlight main outcomes, and finally, 7 CT[21-27] were selected, with 620 samples for meta-analysis (Figure 1 and Table I).

An Evaluation of the Quality of the Methodology Used in the Literature

Among the seven clinical control studies[21-27] contained in this meta-analysis, baseline patient status was reported in all of them. Randomization was mentioned in all pieces of literature, but the methods were not described in detail in 3 of them[18,19,21]. Some literature achieved implied distribution, so the selectivity bias was low. Blinded studies were not mentioned in any literature, which resulted in a low implementation bias. A risk of bias could exist because all literature did not provide detailed information about how many or why studies were lost to follow-up or had to withdraw. Some of the literature was not available for their trial plans, and therefore, the risk was considered uncertain. No other risks were reported, so the bias level was low. In Figures 2 and 3, we can see the results of our risk bias analysis.

Meta-Analysis Result

ORR

There were 7 clinical controlled studies[21-27] with 620 samples contained in this study. The ORR was analyzed. The results of the heterogeneity test indicated that $Chi^2 = 9.48$, $df = 6$, $p = 0.15$, $I^2 = 37\%$, indicating that clearly heterogeneous research data were found in the study. The fixed effect model was adopted to analyze that the objective remission rate after treatment in the study group was remarkably higher ($p < 0.05$, Figure 4).

One-year survival rate

This study contained 7 clinical control studies with 620 samples. The one-year survival rate was analyzed by meta. The results of heterogeneity test indicated that $Chi^2 = 0.42$, $df = 2$, $p = 0.81$, $I^2 = 0\%$, suggesting that clearly heterogeneous research data were found in the study, which were analyzed by the fixed effect model (Figure 5). Study participants' survival rate after one year was remarkably higher ($p < 0.05$).

Overall survival (OS)

A meta-analysis was performed on the OS. The results of the heterogeneity test indicated that $Chi^2 = 8.53$, $df = 1$, $p = 0.003$, $I^2 = 88\%$, indicating that clearly heterogeneous research data were found in

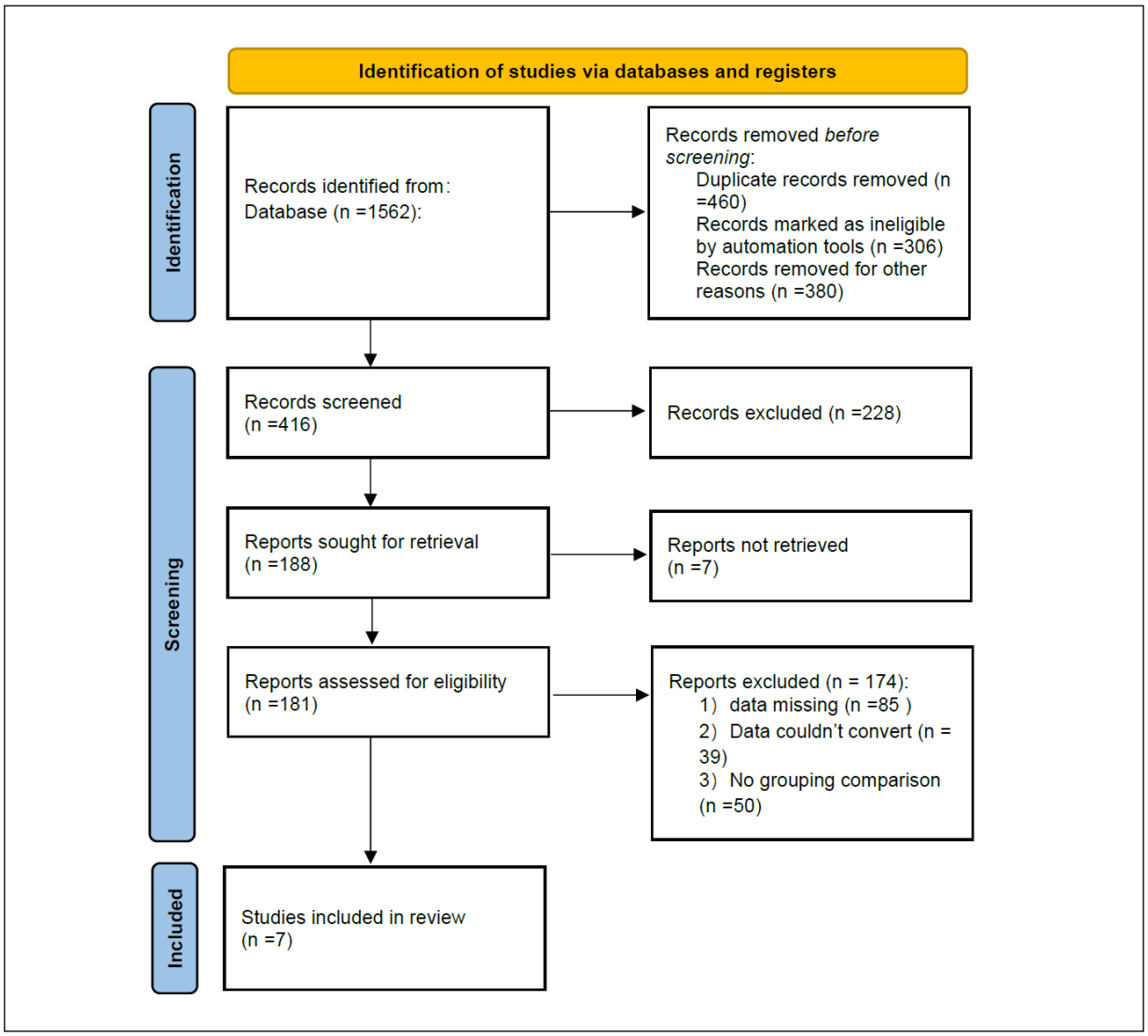


Figure 1. Illustration of literature screening.

the study. The random effect model was used to analyze OS (Figure 6). Despite a higher OS in the study group after treatment, no statistically significant difference was observed ($p > 0.05$).

Progression-free survival (PFS)

Meta-analysis was performed on the PFS. The results of the heterogeneity test indicated that $Chi^2 = 0.56$, df = 1, $p = 0.45$, $I^2 = 0\%$, indicating that clearly heterogeneous research data were found in the study. Using the fixed effect model, we found that the PFS of the study group was remarkably longer ($p < 0.05$, Figure 7).

Adverse events of special interest (AEs)

In clinical practice, AEs of grade 3 or higher required special intervention, or dose reduction or even discontinuation. Meta-analysis of AEs above grade 3 was conducted. The fixed effect model was used for analysis (Figure 8). As can be seen, there was no noticeable difference in the incidence of AEs ($p > 0.05$). This suggested that the combination of targeted therapy and adjuvant chemotherapy did not remarkably increase the risk of AEs ≥ 3 in TNBC patients.

Publication Bias Analysis

Funnel plots were drawn based on ORR, 1-year survival rate, OS, PFS, and AEs of grade 3 or above for the two groups of patients, respectively, and publication bias analysis was performed (Figures 9-13). The results indicated that the

Table I. Basic characteristics of literature.

Include the literature	Year of publication	N (C/T)	Grouping		Outcome index	Research type	Grouping method	Blind method
			C	T				
Liu et al[21]	2019	42/42	TAC Chemotherapy regimen	TAC Chemotherapy regimen plus cetuximab	①②⑤	Forward-looking	Random number table method	No
Yi[22]	2022	56/56	Capecitabine	Capecitabine + apatinib	①②③⑤	Forward-looking	Different treatment methods	No
Wang et al[23]	2021	52/52	Apatinib mesylate	Apatinib mesylate + capecitabine	①④⑤	Forward-looking	Different treatment methods	No
Ye[24]	2013	40/40	Ritecan + carboplatin	Ritecan + carboplatin + capecitabine	①⑤	Forward-looking	Random grouping	No
Nie et al[25]	2021	40/40	Capecitabine	Capecitabine + bevacizumab	①④⑤	Forward-looking	Different treatment methods	No
Zheng[26]	2021	40/40	ET Chemotherapy regimen	ET Chemotherapy regimen + bevacizumab	①⑤	Forward-looking	Random grouping	No
Guo[27]	2021	40/40	TAC Chemotherapy regimen	TAC Chemotherapy + cetuximab	①②⑤	Forward-looking	Random grouping	No

C: control group; T: research group; ① Clinical Response Rate (ORR); ② Survival rate; ③ Overall survival (OS); ④ Progression Free Survival (PFS); ⑤ Adverse reaction.

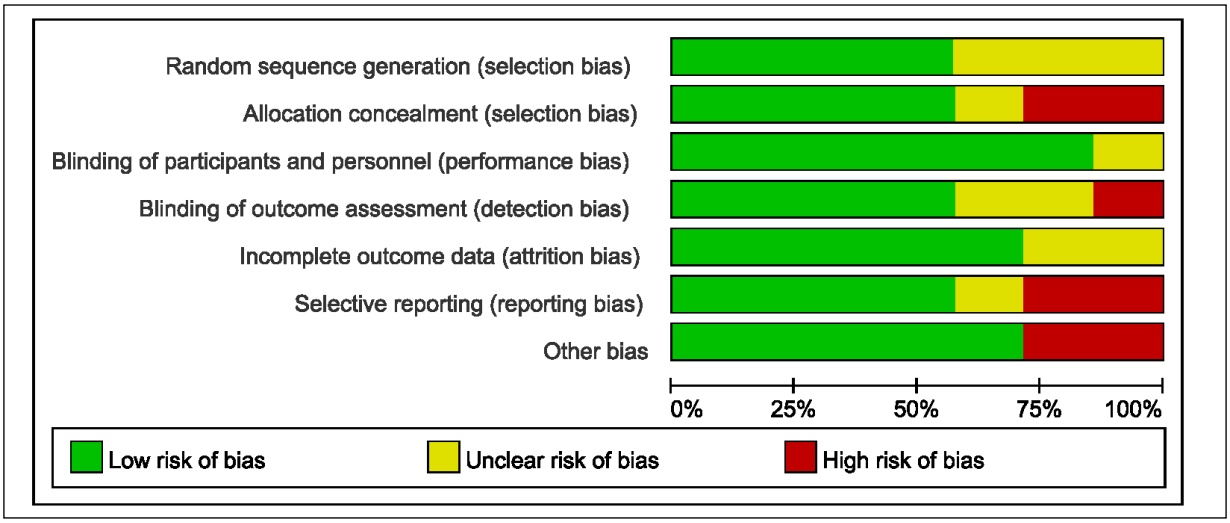


Figure 2. Risk bias chart.

majority of the funnel plots were symmetrically distributed, with a small proportion being asymmetrically distributed, indicating some publication bias in the contained literature. This may be related to the heterogeneity of the studies and the small number of contained literature.

Discussion

TNBC usually occurs in young women, and its etiology is complex[28]. Most patients with advanced cancer are accompanied by cancer cell metastasis, and all of them have been treated with surgery or radiotherapy and chemotherapy. Long-term invasive operation damages the physiological function of the patients, which is prone to the phenomenon of multidrug resistance during the treatment. There is a high mortality rate and a poor prognosis for TNBC. It accounts for 10%-20% of newly diagnosed breast cancers, and the disease is characterized by poor differentiation and rapid proliferation[29]. Compared with the hormone receptor (HR)-positive breast cancer, the recurrence pattern of TNBC is different. The progression and recurrence of TNBC usually occur within 3 to 5 years after diagnosis and is more likely to metastasize to the brain and lung[30].

Previous scholars[30] have shown that cells deficient in *BRCA1* or *BRCA2* are more sensitive to PARP inhibitors. Due to the correlation between TNBC and *BRCA* gene mutations, PARP inhibition agent indicated higher sensitivity in TNBC patients. PARP inhibitors currently undergoing clinical trials include iniparib, olaparib, and ve-

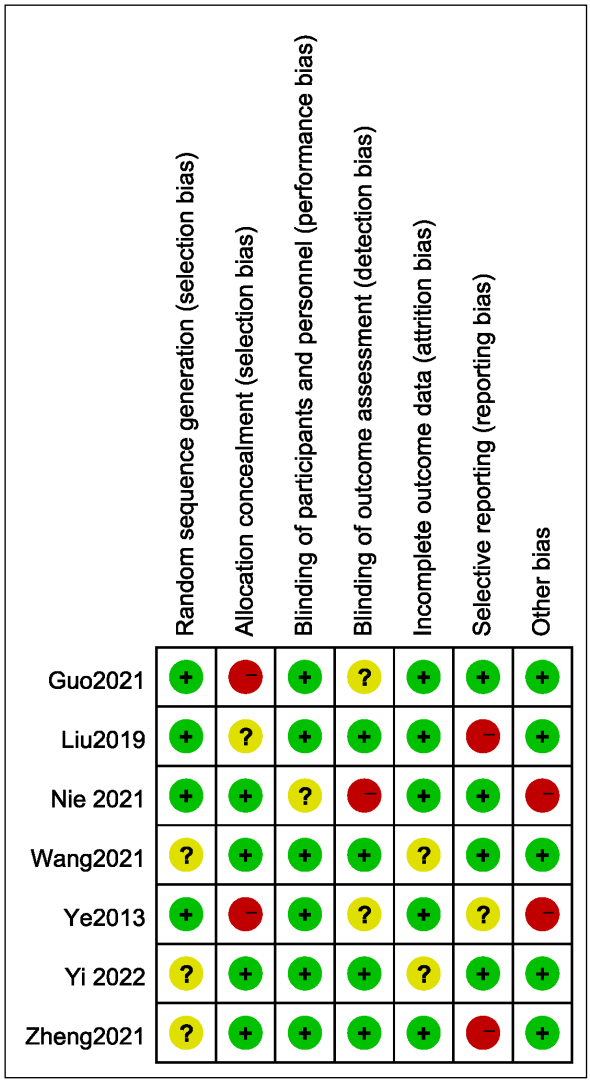


Figure 3. Summary chart of risk bias.

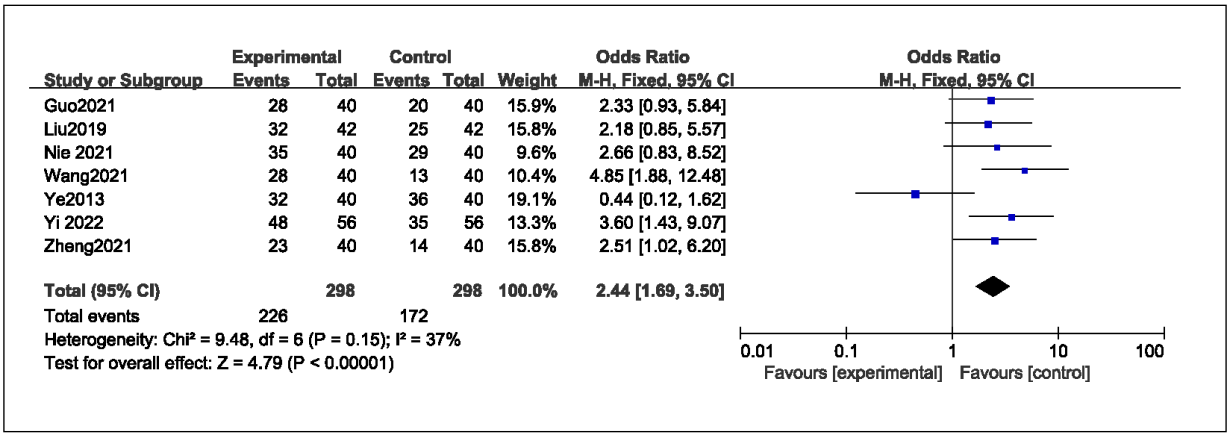


Figure 4. Meta-analysis forest map for the comparison of two groups of ORR rates.

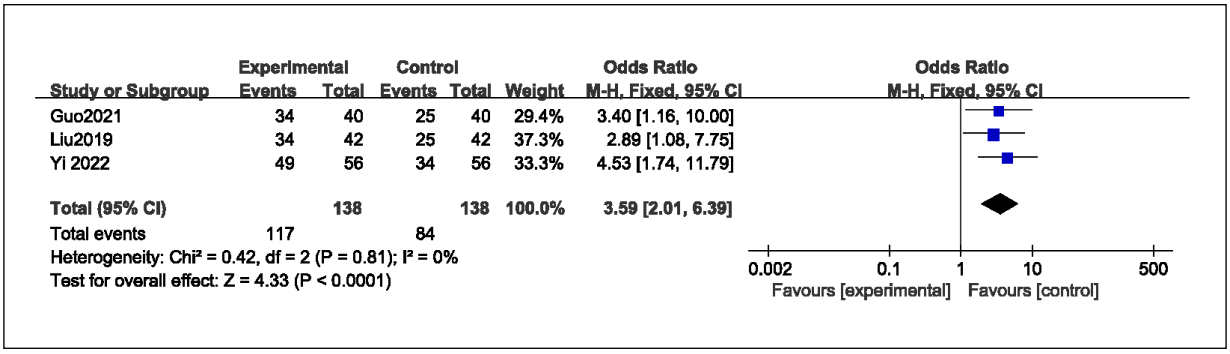


Figure 5. Meta-analysis forest map of comparison of 1-year survival rate between two groups.

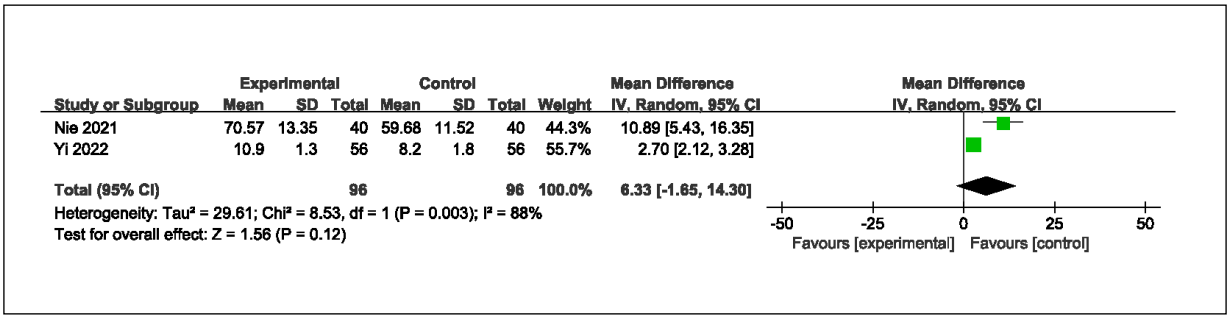


Figure 6. Meta-analysis forest map of two groups of total survival time comparison.

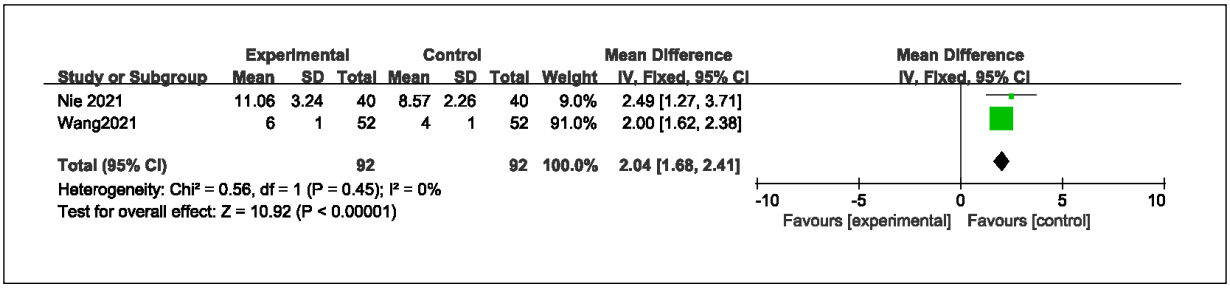


Figure 7. Meta-analysis forest map for comparison of PFS between two groups.

liparib. The results of a phase II clinical trial[31] for patients with advanced TNBC indicated that compared with chemotherapy alone with gemcitabine and carboplatin, the combination of iniparib could remarkably improve the clinical benefit rate (CBR) and PFS. A remarkable difference in the incidence of AEs was not observed[31]. The phase III clinical trial conducted by O'Shaughnessy et al[32] also assessed the efficacy of gemcitabine and carboplatin associated with enipanil when treating advanced TNBC, but the results indicated that PFS and OS did not improve remarkably. In a study on ompanib monotherapy in patients with advanced breast cancer with BRCA1/2 gene mutations[33], the subjects were divided into two groups, including oral orapanil 400 mg twice a day and 100 mg twice a day. The results indicated that the ORR was 41% and 22%, respectively. The median PFS was 5.7 months and 3.8 months, respectively. This trial[33] has provided evidence for the application of PARP inhibitors in breast cancer with *BRCA* deficiency.

Some studies[34] have found that the expression level of vascular endothelial growth factor

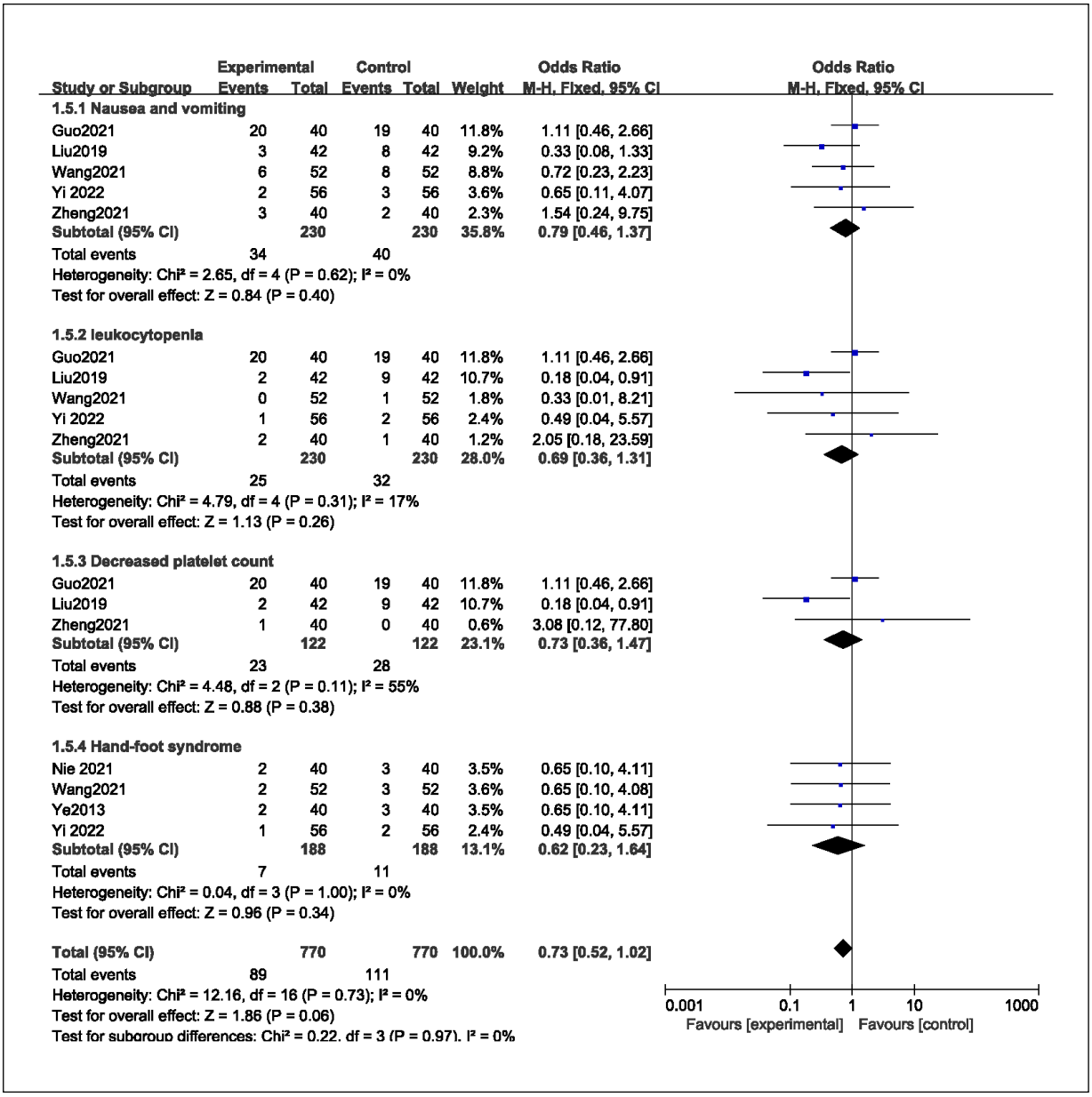


Figure 8. Meta-analysis forest map of two groups of AEs above level 3.

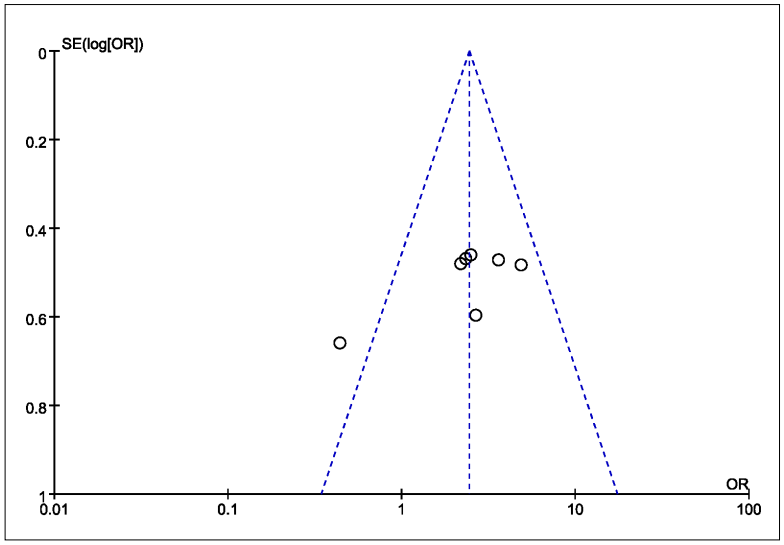


Figure 9. Funnel chart based on ORR rate.

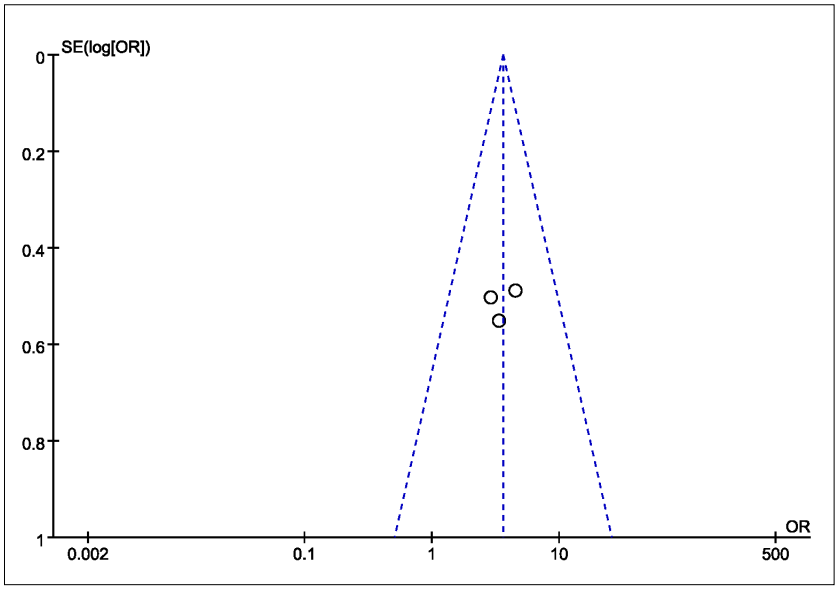


Figure 10. Funnel chart based on 1-year survival rate.

(VEGF) in TNBC patients is remarkably higher compared to non-TNBC patients. At present, many clinical trials[35,36] have studied the application of anti-angiogenic monoclonal antibody bevacizumab when treating TNBC. According to the E2100 trial[35], bevacizumab paired with paclitaxel reduced the risk of disease progression by 51% and doubled median progression-free survival for patients with advanced TNBC. The International large-scale Phase III clinical trial[36] found that standard chemotherapy associated with bevacizumab could increase PFS in TNBC patients from 6.0 months to 8.2 months. The above studies[35,36] have shown that the combination of bevacizumab can prolong the PFS of TNBC patients but did not find a trend to prolong the overall survival. Regarding second-line treatment, the results of the RIBBON-2 trial[37] indicated that the median PFS of the placebo group and the combined bevacizumab group were 5.1 months and 7.2 months, respectively, ORR increased by 10%, and median OS was also an extended trend. This trial[37] has suggested that bevacizumab may provide clinical benefit in the second-line treatment of TNBC.

There were 620 samples included in the seven case-control studies[21-27] in this meta-analysis. PFS, ORR, and 1-year survival rates were

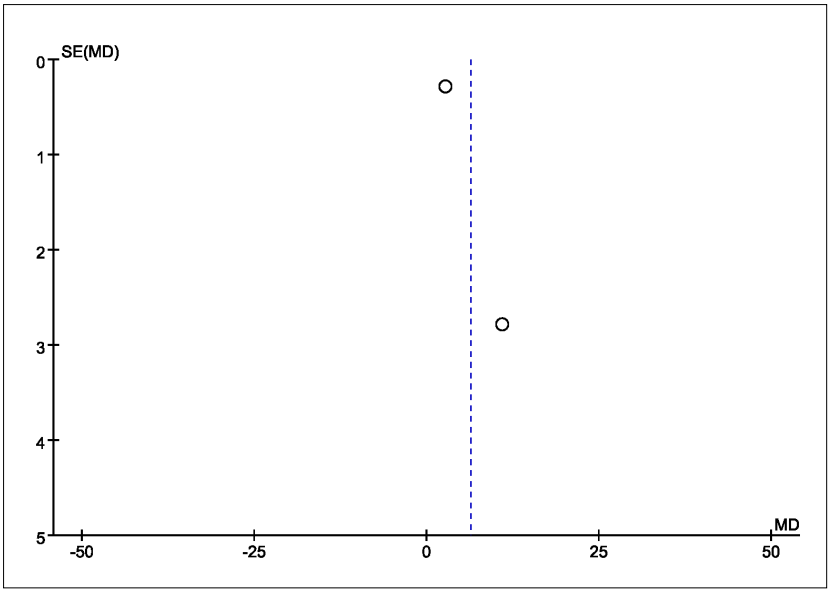
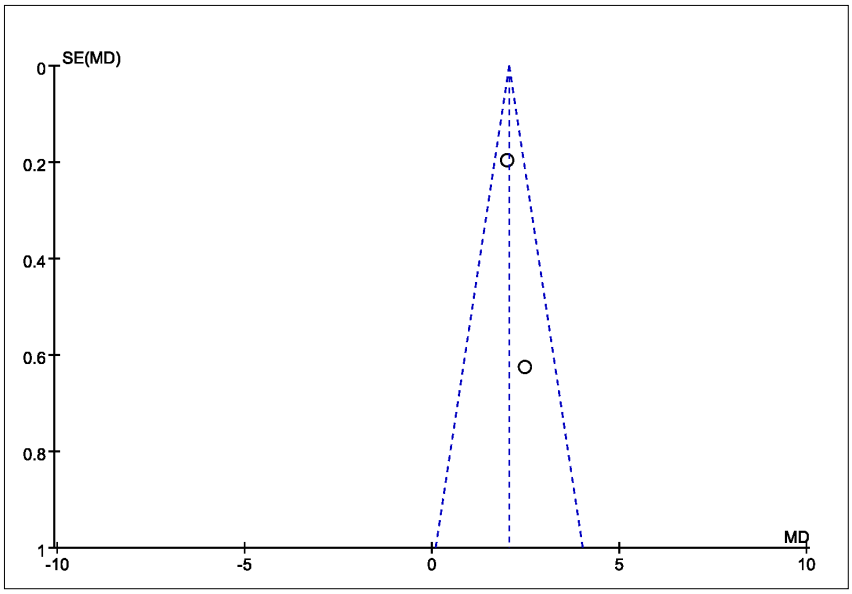


Figure 11. Funnel diagram based on OS time.

remarkably higher in the study group. This indicated that targeted therapy associated with adjuvant chemotherapy can remarkably improve the ORR rate and 1-year survival rate of TNBC patients, and prolong PFS, which is consistent with the results reported in previous studies[38]. Furthermore, the OS of the study group was higher after treatment. This has shown that compared with adjuvant chemotherapy alone and single targeted therapy, targeted therapy associated with adjuvant chemotherapy can remarkably relieve symptoms and improve survival rate in patients with TNBC but has no remarkable effect on OS in patients with TNBC. As a general rule, targeted therapy combined with adjuvant chemotherapy is more beneficial than either targeted therapy alone or adjuvant chemotherapy alone. Patients' conditions and short-term survival rates are more beneficial if they are improved. However, the impact of these three treatments on the long-term survival rate of patients is consistent. In the future, we need to explore a more efficient treatment, in order to protect the life and safety of patients better.

At the same time, it is an important link in clinical work to master the type and degree of

Figure 12. Funnel diagram based on PFS.



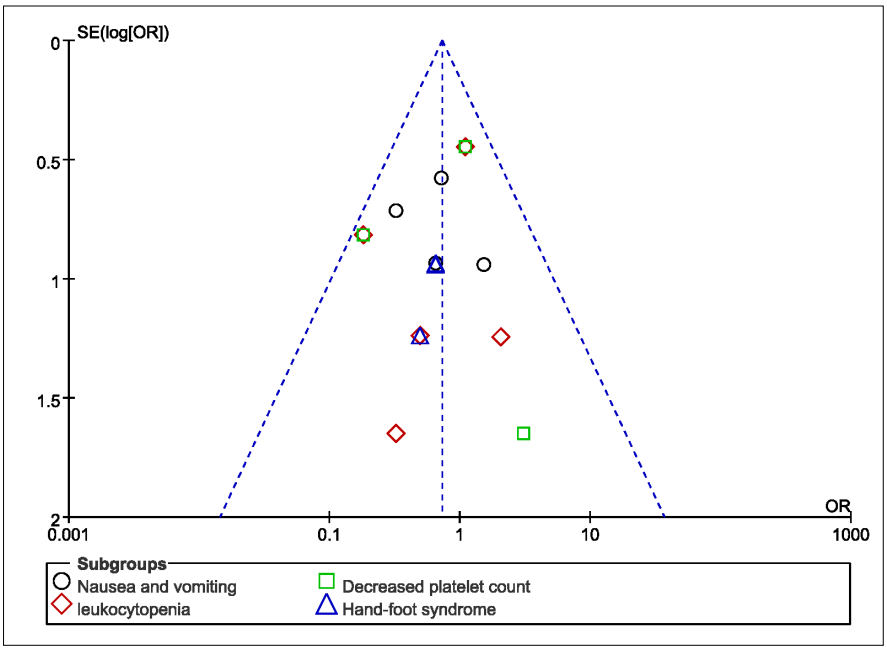


Figure 13. Funnel chart based on level 3 and above AEs.

AEs of targeted therapy. Among the AEs, the most common AEs in the combined treatment group were grade 1 to grade 2, which could be alleviated or disappeared after corresponding symptomatic treatment. It should be noted that grade 3 or above AEs require special intervention or dose reduction or even withdrawal, such as nausea and vomiting, hand and foot syndrome, leukopenia, and thrombocytopenia. Most of the AEs can be controlled by suspending administration and considering the use of corticosteroids. The principles for dealing with more serious AEs are early detection, early evaluation, and early treatment. Meta-analysis of grade 3 AEs indicated that there were no remarkable differences in the incidence of AEs. This has suggested that targeted therapy associated with adjuvant chemotherapy cannot remarkably increase the risk of developing 3 or more AEs in patients with TNBC, and the incidence of AEs is similar to that of patients who only use adjuvant chemotherapy or targeted therapy. In previous studies[39], a small number of patients had AEs of a manageable range. The probability of AEs is low, and the severity is mild. After systematic symptomatic treatment, the AEs of most patients can be alleviated. In addition, funnel plots were plotted according to ORR, 1-year survival, OS, PFS, and grade 3 AEs. The results indicated that most of the funnel maps were symmetrical, and a few were asymmetrical, suggesting that there was a certain publication bias in the contained literature, which may be related to the heterogeneity of the study and the small number of contained literature.

In addition, due to the limited number of literature and sample size included in this study, there is inevitably bias in the research results. Therefore, in future research, we will continue to pay attention to relevant clinical research results and supplement them in this research project, in order to obtain more reliable and convincing research data.

Conclusions

Targeted therapy associated with adjuvant chemotherapy can remarkably improve the outcome of patients with advanced TNBC, prolonging their PFS and OS without increasing adverse effects. The validity of this research, however, will require higher quality studies and longer follow-ups.

Data Availability

The data used for this study have been included in the manuscript.

Acknowledgments

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Ethics Approval
Not applicable.

Informed Consent
Not applicable.

Conflicts of Interest
The authors declare that they have no competing interests.

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This study did not receive any funding in any form.

Authors' Contributions
(X.-D. Su) Xiandu Su conceived the study design and the content concept; (J.-G. Li) Jingui Li, (A.-X. Zhao) Aixia Zhao, performed the data collection, extraction and analyzed the data; (Z.-Q. Tian) Zhongqiu Tan, (L.-M. Li) Linmao Li interpreted and reviewed the data and drafts; (P. Huang) Peng Huang reviewed the final draft.

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