Effect of neoadjuvant chemotherapy in patients with triple-negative breast cancer: A meta-analysis

MUYOU TIAN[1,2], YAHUA ZHONG[1,2], FUXIANG ZHOU[1,2], CONGHUA XIE[1,2], YUNFENG ZHOU[1,2] and ZHENGKAI LIAO[1,2]

[1]Hubei Cancer Clinical Study Center, Hubei Key Laboratory of Tumor Biological Behaviors; [2]Department of Radiation Oncology and Medical Oncology, Zhongnan Hospital, Wuhan University, Wuhan, Hubei 430071, P.R. China

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Abstract. The present meta-analysis aimed to evaluate the effect of neoadjuvant chemotherapy on pathological complete response (pCR) and survival rate in patients with triple-negative breast cancer (TNBC). Specific inclusion and exclusion criteria were used to conduct a search of the available databases, in order to find studies performed between January 2006 and January 2014. The bibliographies of the included studies were examined with the same criteria. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group framework was used to evaluate the included studies, and RevMan 5.1 and GRADEprofiler 3.6 were used to analyze the extracted data. A total of 19 studies with 6,180 patients were included. The meta-analysis revealed that the pCR rates in patients with TNBC were significantly higher than those in patients with non-TNBC. The 5-year disease-free survival (DFS) and overall survival (OS) rates were significantly lower in the patients with TNBC compared with those with non-TNBC. Furthermore, these survival rates were significantly higher in the patients with TNBC who achieved a pCR compared with those in the patients who did not achieve a pCR. pCR rates were higher among the patients with TNBC with high Ki-67 expression than among those with low Ki-67 expression. The patients with TNBC exhibited lower survival rates compared with those with non-TNBC, but achieved higher pCR rates. Moreover, those patients achieving a pCR exhibited improved 5-year survival rates, suggesting that the pCR rate could be predictive of survival in patients with TNBC. In addition, high Ki-67 expression may predict the likelihood of a pCR. However, future multicenter randomized controlled trials are required to enhance the quantity and quality of the clinical evidence.

Correspondence to: Dr Zhengkai Liao, Department of Radiation Oncology and Medical Oncology, Zhongnan Hospital, Wuhan University, 169 Donghu Road, Wuhan, Hubei 430071, P.R. China
E-mail: zliao@whu.edu.cn

Key words: triple-negative breast cancer, neoadjuvant chemotherapy, pathological complete response, survival, molecular marker

Introduction

Breast cancer is subdivided into five types, namely luminal A, luminal B, human epidermal growth factor receptor-2 (HER-2)-positive, normal-like and basal-like breast cancer, according to cellular-molecular phenotype (1). In total, ~90% of triple-negative breast cancer (TNBC) cases are classified as basal-like. TNBC, as its name suggests, has an estrogen receptor (ER)-negative, progesterone receptor (PR)-negative and HER-2-negative phenotype, and accounts for 15% of all breast cancer cases. TNBC is highly aggressive, with a high propensity for metastasis and a poor survival rate (2,3). Therefore, endocrine and molecularly targeted therapies are unsuitable for patients with TNBC, and chemotherapy is the only systemic therapy available.

Neoadjuvant chemotherapy (NAC) has become a widely applied treatment for early-stage breast cancer (4). NAC can downstage a tumor, potentially enabling breast-conserving surgery for patients who may have otherwise required mastectomy (5,6). Based on preclinical studies in animal models, it was hypothesized that NAC may diminish the micrometastases of breast cancer (7). In general, tumor size and lymph node number are the foremost prognostic predictors of solid tumors following systemic therapy, but they are not appropriate for determining the response to NAC. A pathological complete response (pCR) is used as a short-term evaluation index for the efficacy of NAC.

Patients with TNBC usually achieve a higher pCR rate (8,9). Furthermore, it has been reported that patients with TNBC and those with non-TNBC who achieved pCR following NAC have similar long-term survival rates. By contrast, the 5-year disease-free survival (DFS) rates of patients who did not achieve pCR following NAC differed significantly between those patients with TNBC and those with non-TNBC (10). However, a meta-analysis in 2011 reported that pCR is an independent prognostic factor of overall survival (OS), DFS and relapse-free survival (RFS) for patients with TNBC (11). Other studies indicated that molecular biomarkers, including Ki-67 antigen, tumor suppressor p53, epidermal growth factor receptor (EGFR), and cytokeratin (CK)5 and 6, may predict the pCR rate of patients with TNBC following NAC (12,13).

In this meta-analysis, data was extracted and the short-term efficacy (pCR) and long-term survival (DFS and OS) rates of patients with TNBC treated with NAC were analyzed. In order to provide prognostic guidance for TNBC patients, the present meta-analysis attempted to further prove the association between pCR and long-term survival, and to determine if any biomarkers were predictive of the pCR rate.

Materials and methods

Inclusion and exclusion criteria. Prospective or retrospective controlled trials were included, regardless of the allocation, concealment or blinding. All the following criteria had to be met for inclusion in the meta-analysis: i) NAC must have been the primary initial therapy; ii) patients must have had stage I-III breast cancer; iii) immunohistochemical staining should have confirmed hormone receptor status and/or fluorescence *in situ* hybridization should have confirmed HER-2 status; and iv) the pCR rate, and DFS or OS rates had to have been reported. Studies were excluded if they met any of the following criteria: i) Repetitive publication; ii) small sample size; iii) abstract only; and iv) no sufficient raw data and data unavailable on request.

Literature search strategy. TNBC is a concept that was initially introduced in 2006 (14); therefore, searches of the PubMed database, the China Knowledge Resource Integrated Database, the China Science and Technology Journal Database, and the WanFang database were performed using date limits of between January 2006 and January 2014. Papers in the Chinese and English languages were searched. Retrieval keywords included i) triple-negative breast cancer or TNBC; ii) neoadjuvant chemotherapy or NAC; iii) pathological complete response or pCR; iv) survival or disease-free survival or DFS or overall survival or OS; v) molecular marker or CK5/6 or p53 or Ki-67; and vi) combinations of these terms, including i)+ii), i)+ii)+iii), i)+ii)+iv) and i)+ii)+v).

Data extraction. Based on the aforementioned strategies, studies were selected and their eligibility was confirmed by three independent researchers. The following information was extracted from each study: Authors' names, year of publication, study type, total number of patients, median patient age, primary tumor-node-metastasis (TNM) stage, NAC regimen and survival data.

Quality evaluation. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group framework was used to evaluate the collated data; accordingly, high, medium, low or very low grades were awarded with regard to quality. Randomized controlled trials were considered to be of a high grade, but the following factors were also considered: Risk of bias, indirectness, inconsistency, imprecision and publication bias. Case-control and cohort studies were considered to be of a medium grade.

Statistical analyses. Review Manager software (RevMan, version 5.1 for Windows; The Cochrane Collaboration, Oxford, UK) was used to conduct the meta-analysis. Odds ratio (OR) and 95% confidence interval (95% CI) values were calculated. A χ^2 test was used to evaluate heterogeneity in the data. The fixed-effects model was used for studies without significant heterogeneity ($I^2 \leq 50\%$ or $P \geq 0.10$), whereas the random-effects model was used for studies with significant heterogeneity. Funnel plots were generated using RevMan to detect publication bias. GRADEpro software (version 3.6 for Windows; The Cochrane Collaboration) was used to conduct the quality evaluation.

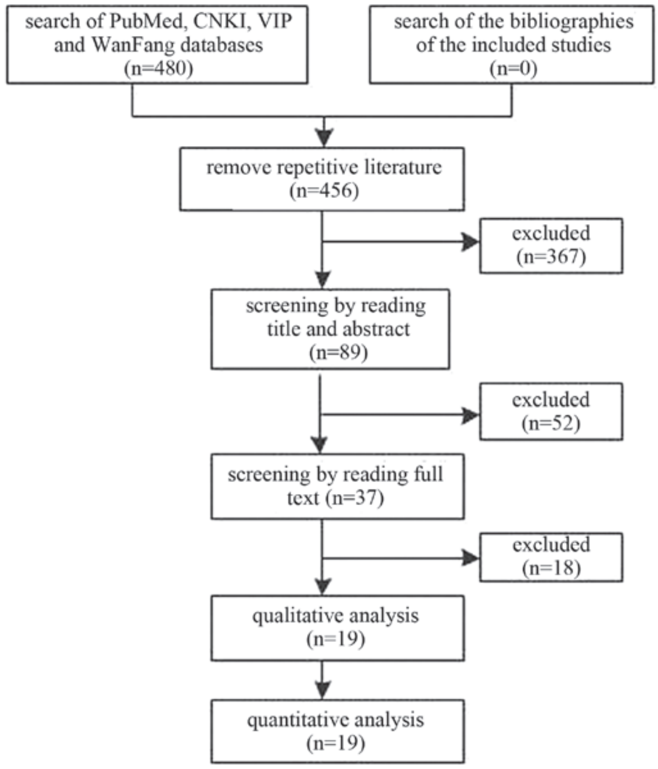

Figure 1. Flow-chart of the literature search process. CNKI, China Knowledge Resource Integrated database; VIP, China Science and Technology Journal database.

Results

Eligible studies and data summary. A total of 480 studies were first identified for evaluation. Based on the criteria described in the methods, 19 publications were eligible for inclusion in the present meta-analysis (10,12,15-31). The bibliographies of these 19 publications were also searched, but this did not provide further studies for inclusion. Therefore, a final total of 19 studies with 6,180 patients were included. The search process is described in Fig. 1. The anthracycline-based and/or paclitaxel regimens were the most common NAC regimens applied. Table I describes the characteristics of the eligible studies in more detail.

pCR in patients with TNBC and non-TNBC. A total of 13 stu dies (10,15-20,24,25,27-30) reported the pCR rates in patients with TNBC and non-TNBC who received NAC. There was no heterogeneity between the results of different studies ($I^2=23\%$, $P=0.21$), so the fixed-effects model was applied for data analysis. The pCR rates in the patients with TNBC were significantly higher than those in the patients with non-TNBC (OR, 3.10; 95% CI, 2.51-3.82; Fig. 2).

Table I. Characteristics of eligible studies.

First author, year (ref.)	Study types	Total patients, n	Median age, years	Stages	NAC regimens[a]
Bidard *et al,* 2008 (18)	Retrospective	293	50	I-III	FEC or FAC x(4-6)
Chang *et al,* 2010 (19)	Prospective	74	49	II-III	TC x4
Darb-Esfahani *et al,* 2009 (20)	Prospective	913	-	II-III	AT x4, or AC x4 + docetaxel x4
Fisher *et al,* 2012 (21)	Retrospective	385	50	I-III	-
Frasci *et al,* 2009 (22)	Prospective	74	48	II-III	AT+cisplatin x8
Medioni *et al,* 2011 (27)	Prospective	74	50	II-III	Docetaxel+gemcitabine x2, or vinorelbine+epirubicin x2
Keam *et al,* 2011 (23)	Prospective	105	-	II-III	Docetaxel or Adriamycin x3
Li *et al,* 2011 (24)	Retrospective	316	50	I-III	CAF+taxanes
Li *et al,* 2011 (12)	Prospective	220	48	II-III	AT x(4-6)
Liedtke *et al,* 2008 (25)	Prospective	1118	48	I-III	FAC/FEC/AC, or TFAC/TFEC, or Single-agent taxane
Masuda *et al,* 2011 (26)	Prospective	163	50	I-III	FEC x4, or AT x4
Ono *et al,* 2012 (28)	Prospective	474	53	II-III	AC/AT/CEF
Tang *et al,* 2012 (29)	Retrospective	198	-	I-III	CEF/CMF/paclitaxel
Wu *et al,* 2011 (30)	Retrospective	249	47	II-III	AT x4
Yoo *et al,* 2012 (31)	Retrospective	276	44	I-III	-
Jia *et al,* 2012 (17)	Retrospective	249	47	II-III	ET
Sun *et al,* 2009 (15)	Prospective	326	47	II-III	CTF x4
Wang and Gao, 2010 (16)	Retrospective	535	45	I-III	FEC x4
Zhou *et al,* 2009 (10)	Retrospective	138	51	II-III	AT x4

[a]'x' indicates number of cycles (e.g. x4, four cycles). FEC, cyclophosphamide+epirubicin+fluorouracil; FAC, cyclophosphamide+Adriamycin+fluorouracil; TC, docetaxel+cyclophosphamide; AT, Adriamycin+docetaxel; ET, epirubicin+docetaxel; AC, Adriamycin+docetaxel; CAF, cyclophosphamide+Adriamycin+fluorouracil; CEF, cyclophosphamide+epirubicin+fluorouracil; CTF, cyclophosphamide+docetaxel+fluorouracil; TFAC, docetaxel+FAC; TFEC, docetaxel+FEC.

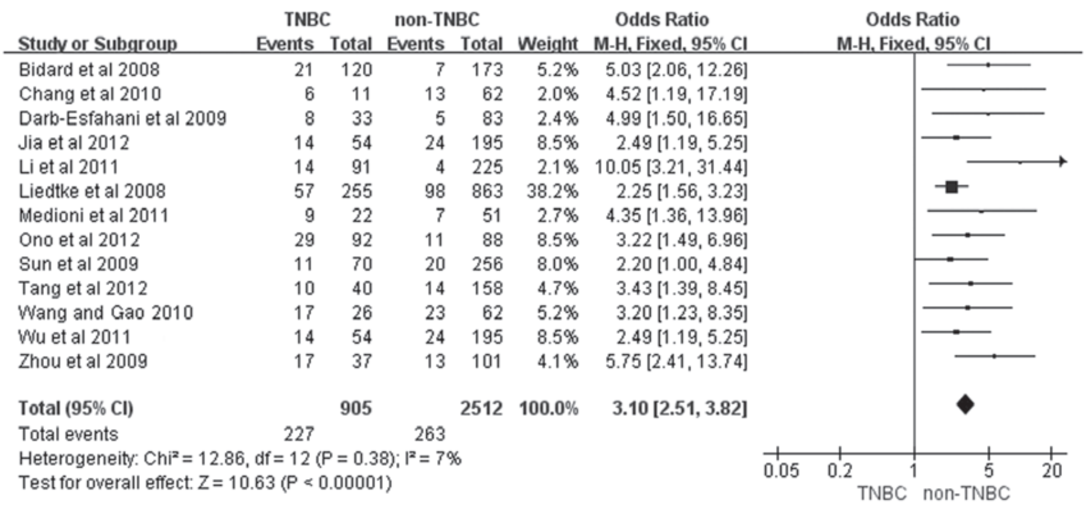

Figure 2. Forest plot: Pathological complete response rate in patients with TNBC and non-TNBC who received neoadjuvant chemotherapy. TNBC, triple-negative breast cancer; CI, confidence interval.

Survival in patients with TNBC and non-TNBC. A total of 6 studies (10,16,17,24,25,30) reported the 5-year DFS rate in patients with TNBC or non-TNBC who received NAC. There was significant heterogeneity between the different research results (I^2=65%, P=0.01), so the random-effects model was applied for data analysis. The 5-year DFS rate in the patients with TNBC was significantly lower than that in the patients with non-TNBC (54.6 vs. 70.8%; OR, 0.53; 95% CI, 0.34-0.81; Fig. 3).

A total of 7 studies (10,15-17,24,25,30) reported the 5-year OS rate in patients with TNBC or non-TNBC who received NAC. There was no heterogeneity between the results of the different studies (I^2=5%, P=0.39), so the fixed-effects model was applied

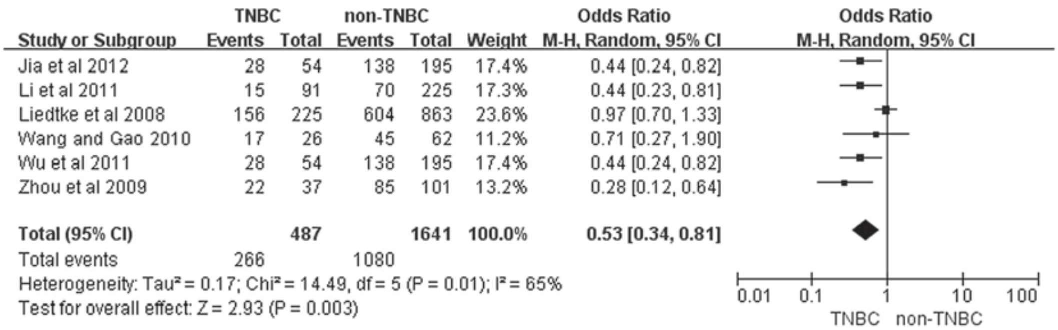

Figure 3. Forest plot: 5-year diseasae-free survival rates in patients with TNBC and non-TNBC who received neoadjuvant chemotherapy. TNBC, triple-negative breast cancer; CI, confidence interval.

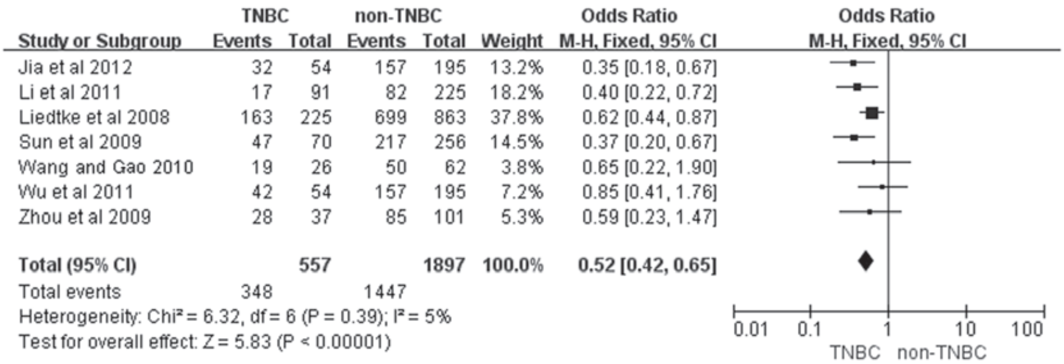

Figure 4. Forest plot: 5-year overall survival rates in patients with TNBC and non-TNBC who received neoadjuvant chemotherapy. TNBC, triple-negative breast cancer; CI, confidence interval.

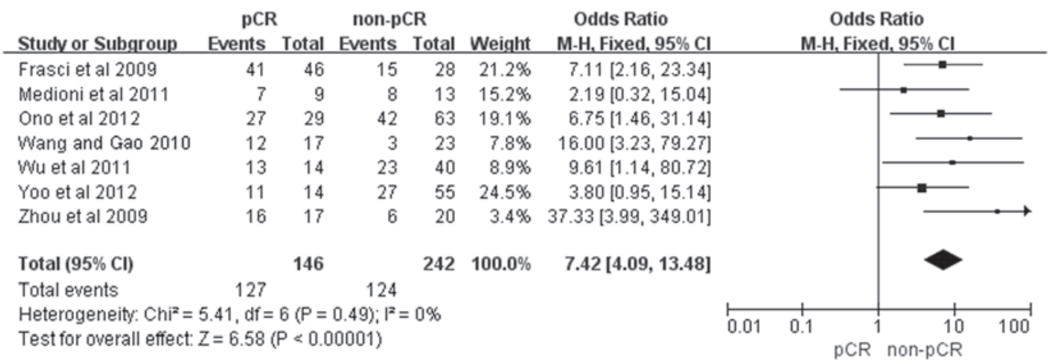

Figure 5. Forest plot: 5-year disease-free survival rates in patients with triple-negative breast cancer who received neoadjuvant chemotherapy according to the achievement of a pCR. CI, confidence interval; pCR, pathological complete response.

for data analysis. The 5-year OS rate in the patients with TNBC was significantly lower than that in the patients with non-TNBC (62.5 vs. 80.7%; OR, 0.52; 95% CI, 0.42-0.65; Fig. 4).

Survival rate of patients with TNBC as a function of pCR. For the 7 studies (10,16,22,27,28,30,31) that reported the 5-year DFS rate in the patients with TNBC who received NAC according to the achievement of a pCR, there was no heterogeneity between the results (I^2=0%, P=0.49), therefore, the fixed-effects model was applied for data analysis. The 5-year DFS rate was significantly higher among the patients with TNBC who achieved a pCR than among those who did not achieve a pCR (OR, 7.42; 95% CI, 4.09-13.48; Fig. 5).

For the 7 studies (10,16,21,22,27,30,31) that reported the 5-year OS rate in patients with TNBC who received NAC according to the achievement of a pCR, there was also no heterogeneity between the results (I^2=0%, P=0.59), therefore, the fixed-effects model was applied for data analysis. The 5-year OS rate was significantly higher among the patients with TNBC who achieved a pCR than among those who did not achieve a pCR (OR, 6.74; 95% CI, 3.63-12.52; Fig. 6).

Association between molecular marker expression and pCR in patients with TNBC following NAC. A total of 6 studies (12,18,20,23,26,28) reported the association between molecular marker expression and the pCR rate in the patients

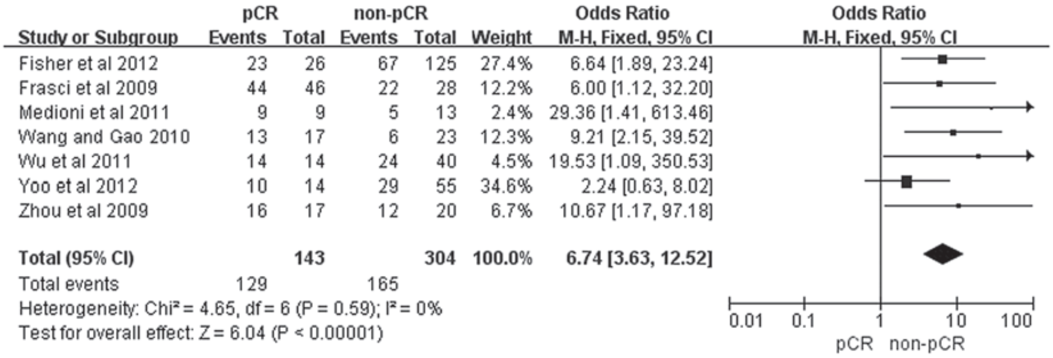

Figure 6. Forest plot: 5-year overall survival rates in patients with triple-negative breast cancer who received neoadjuvant chemotherapy according to the achievement of a pCR. CI, confidence interval; pCR, pathological complete response.

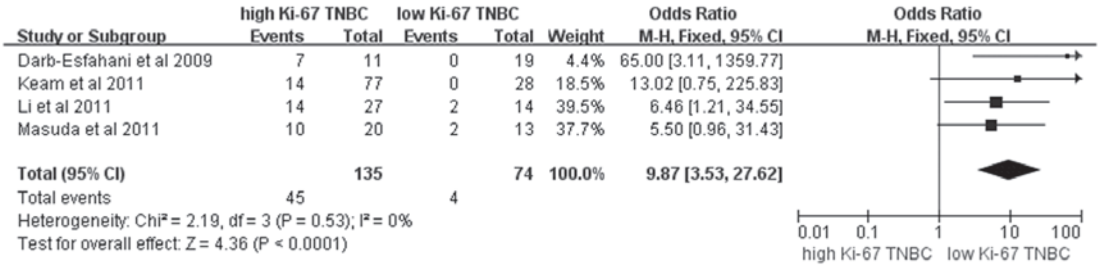

Figure 7. Forest plot: Pathological complete response as a function of the Ki-67 expression level in patients with triple-negative breast cancer who received neoadjuvant chemotherapy. CI, confidence interval.

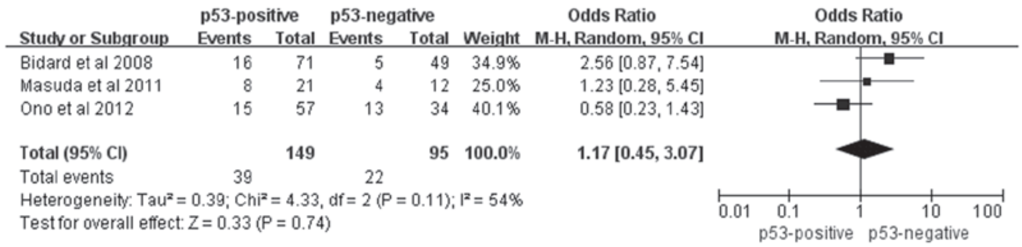

Figure 8. Forest plot: Pathological complete response as a function of the p53 expression level in patients with triple-negative breast cancer who received neoadjuvant chemotherapy. CI, confidence interval.

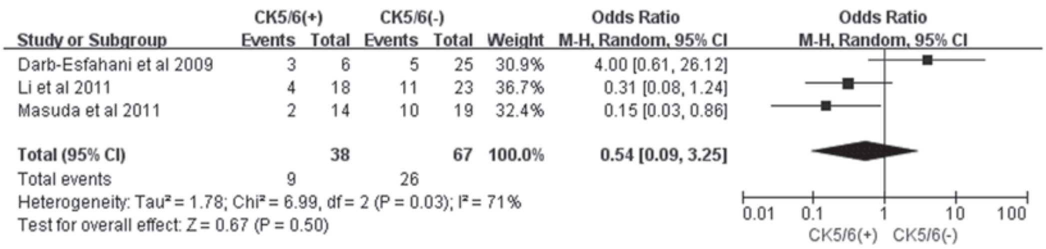

Figure 9. Forest plot: Pathological complete response as a function of the CK5/6 expression level in patients with triple-negative breast cancer who received neoadjuvant chemotherapy. CK, cytokeratin; CI, confidence interval.

with TNBC who received NAC. A pooled study of 4 of these studies (12,20,23,26) showed that the patients with TNBC and high Ki-67 expression achieved significantly higher pCR rates than those with low Ki-67 expression (OR, 9.87; 95% CI, 3.53-27.62; Fig. 7). In addition, two pooled analyses of p53 (18,26,28) and CK5/6 (12,20,26) levels revealed no association between these molecules and pCR rate (P>0.05; Figs. 8 and 9).

Quality evaluation. The quality of the meta-analysis was evaluated using the GRADE framework and is shown in Table II. The quality of the investigation of the 5-year DFS rate in the patients with TNBC with or without a pCR was high. The quality for the study of the 5-year DFS rate in the patients with TNBC or non-TNBC was low. The other assessments were considered to be of moderate quality. The main reason for the lower quality was

Table II. Grading of Recommendations Assessment, Development and Evaluation framework assessment of eligible studies.

Design			Quality assessment					
Outcome	Experiment	Control	Publication bias	Inconsistency	Indirectness	Imprecision	No. of eligible studies	Quality
pCR	TNBC	Non-TNBC	Yes	No	No	No	14	Moderate
5-year DFS	TNBC	Non-TNBC	Yes	No	No	Yes	6	Low
5-year OS	TNBC	Non-TNBC	No	No	No	Yes	7	Moderate
5-year DFS	pCR	Non-pCR	No	No	No	No	7	High
5-year OS	pCR	Non-pCR	Yes	No	No	No	7	Moderate
pCR	High Ki-67	Low Ki-67	Yes	No	No	No	6	Moderate

TNBC, triple-negative breast cancer; DFS, disease-free survival; OS, overall survival; pCR, pathological complete response.

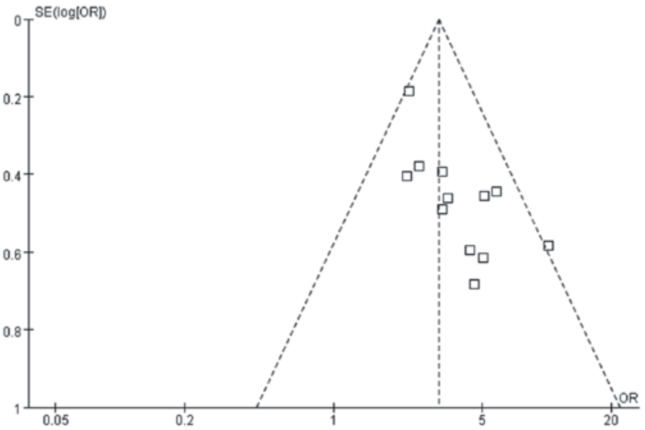

Figure 10. Funnel plot: Pathological complete response in patients with TNBC and non-TNBC who received neoadjuvant chemotherapy. TNBC, triple-negative breast cancer; OR, odds ratio; SE, standard error.

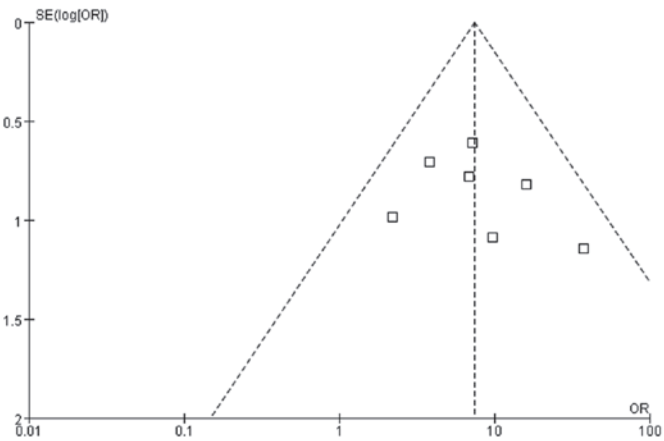

Figure 11. Inverse funnel plot: 5-year disease-free survival rates in patients with triple-negative breast cancer who received neoadjuvant chemotherapy according to the achievement of a pathological complete response. OR, odds ratio; SE, standard error.

publication bias. For example, in Fig. 10, the lower left region of the funnel plot is vacant, with points distributed throughout the remainder of funnel, suggesting a publication bias; this may be due to the difficulty in publishing studies with negative results. In Fig. 11, the points in the inverted funnel plot show homogeneous distribution on each side, suggesting no clear publication bias.

Discussion

Patients with TNBC generally have aggressive cancer with higher metastatic and lower survival rates than those with non-TNBC. However, TNBC patients generally achieve a higher pCR rate following NAC treatment compared with those individuals with other subtypes of breast cancer, as was confirmed by the present meta-analysis. In the current meta-analysis, the 5-year DFS and OS rates of patients with TNBC who received NAC were lower than those of patients with non-TNBC. However, a significant improvement in the 5-year DFS and OS rates was apparent in the patients with TNBC who achieved pCR as a result of NAC treatment, suggesting that NAC significantly improves the survival of patients with TNBC, but only for those who show a pCR to treatment.

Certain studies have suggested that different NAC regimens have a different effect on the pCR in breast cancer patients. For example, patients achieve a higher pCR rate and long-term survival rate when paclitaxel is used in anthracycline-based NAC regimens (8,32). In addition, platinum-based NAC regimens also affect the survival rate (33). The NAC regimens of eligible studies in the present meta-analysis were mostly anthracycline and/or paclitaxel regimens.

TNBC can be classified as chemosensitive or chemoresistant (34), distinguished by an analysis of the tumoral expression of molecular marker genes, including EGFR, CK5/6, cyclooxygenase-2, Y-box binding protein-1, B-cell lymphoma 2, Ki-67 antigen and p53 tumor suppressor. It is generally easier to achieve a pCR in patients with chemosensitive disease, therefore, an analysis of molecular marker expression in patients with TNBC would be useful in predicting the response to NAC. The current meta-analysis showed that patients with TNBC characterized by high levels of Ki-67 antigen expression achieved a higher pCR rate than those with low-level expression, suggesting that Ki-67 could be used as a predictor of prognosis and for the selection of patients who would derive the greatest clinical benefit from NAC. However, more studies are required to confirm the association between Ki-67 and patient prognosis. A clinical trial has reported that patients with TNBC can benefit from chemotherapy combined with molecularly targeted therapy in the form of poly-ADP ribose polymerase inhibition, and more detailed studies are underway (35).

The TNM stages of the patients included in the present meta-analysis were I-III/II-III. Therefore, it is possible that the ambiguity of the cancer stage could have introduced a bias in the data; however, the quality of these studies was considered to be mostly moderate on analysis. In addition, the overall results were reliable despite a certain degree of publication bias.

In summary, despite moderate quality and a certain degree of publication bias, a number of conclusions can be made. The survival rates in the patients with TNBC were significantly lower than those in patients with non-TNBC, but the patients with TNBC achieved a higher pCR rate in response to NAC treatment. Furthermore, the patients with TNBC who achieved a higher pCR rate in response to NAC treatment showed significant improvement in survival rates. Finally, high Ki-67 expression was positively correlated with a higher pCR rate, whereas p53 and CK5/6 expression did not display any prognostic function. Future multicenter randomized controlled trials would provide additional support to the current study and aid in determining whether other molecular markers can act as prognostic factors.

Acknowledgements

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