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Methodological quality evaluation of systematic reviews or meta-analysis of trastuzumab-based therapy for breast cancer

A systematic review

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Abstract

Background: To evaluate the methodological quality of systematic reviews (SRs) or meta-analysis of trastuzumab-based therapy for breast cancer.

Methods: We searched the PubMed, EMBASE, Web of science, Cochrane library, international prospective register of systematic reviews, Chinese BioMedical Literature Database, Wan Fang, China National Knowledge Infrastructure and VIP database for SRs or meta-analysis. The methodological quality of included literatures was appraised by risk of bias in systematic review (ROBIS) tool.

Results: Twenty three eligible systematic reviews or meta-analysis were included. Only 2 systematic reviews provided protocol. The most frequently searched databases were PubMed, MEDLINE, EMBASE, and the Cochrane. The two-reviewers model described in the screening for eligible original articles, data extraction, and methodological quality evaluation had 30%, 61%, and 26%, respectively. In methodological quality assessment, 52% SRs or meta-analysis used the Jadad scoring or Cochrane reviewer' handbook. Research question were well matched to all SRs or meta-analysis in phase 1 and 35% of them evaluated "high" risk bias in study eligibility criteria. The "high" risk of bias in all non-Cochrane SRs or meta-analyses, which involve methods used to identify and/ or select studies. And more than half SRs or meta-analysis had a high risk of bias in data collection and study appraisal. More than two-third of SRs or meta-analysis were accomplished with high risk of bias in the synthesis and findings.

Conclusions: The study indicated poor methodological and reporting quality of SRs/meta-analysis assessing trastuzumab-based therapy for breast cancer. Registration or publishing the protocol and the reporting followed the PRISMA checklist are recommended in future research.

Abbreviations: CBM = Chinese BioMedical Literature Database, CNKI = China National Knowledge Infrastructure, HER2 = human epidermal growth factor receptor 2, NCCN = National Comprehensive Cancer Network, pCR = pathologic response rates, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PROSPERO = International Prospective Register of Systematic Reviews, RCTs = randomized controlled trials, ROBIS = risk of bias in systematic review, SRs = systematic reviews, VIP = China Science and Technology Journal Database.

Keywords: breast cancer, methodological quality, ROBIS, systematic review, trastuzumab

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1. Introduction

Breast cancer is the most common diagnosed malignancy in women. Its incidence rate is the highest and the leading cause of cancer death in women.[1] In the subtypes of breast cancer, overexpression and/or gene amplification of the human epidermal growth factor receptor 2 (HER2) present in 20% to 25% of breast neoplasms, aggressive biological behavior and worse prognosis when compared with HER2 negative tumors.[2–5] Trastuzumab is a HER2-targeted humanized monoclonal antibody that inhibits the proliferation of tumor cells and induces tumor cell death through multiple mechanisms of action. It was approved in 1998 for use in adjuvant and metastatic settings, directly acting on HER2 receptors, revolutionizing the treatment of HER2-positive breast cancer, which is a landmark. Current randomized controlled trials (RCTs) have demonstrated that trastuzumab not only significantly improves survival and response rates in the adjuvant setting,[6–8] but also increases pathologic response rates (pCR) and breast-conserving therapy providing additional clinical benefits in the neoadjuvant setting.[9–11] Therefore, NCCN guidelines recommend that trastuzumab is the standard treatment for HER2-positive breast cancer.[12] A large amount of systematic reviews or meta-analysis has been published to gain a higher-level evidence. Viani et al[13] reported that adjuvant trastuzumab showed a significant reduction of mortality, recurrence, metastases rates, and second tumors other than breast cancer. Cardiac toxicity was 2.45 times higher in trastuzumab arms, but the result existed heterogeneity. Lin et al[14] reported that trastuzumab combined with adjuvant chemotherapy for the treatment of her2-positive early breast cancer can significantly improve the disease-free survival rate of patients and reduce the distant recurrence rate, but there is no significant improvement in the overall survival rate. Valachis et al[15] demonstrated that trastuzumab had no significant difference in breast-conserving surgery for breast cancer, and did not increase the incidence of neutropenia, neutropenic fever, and cardiac adverse events. Although the efficacy results seem to support its use, other controversies have been raised about its net benefit in relation to cardiac toxicity and a long-term increased risk of metastasis to the central nervous system. Due to systematic defects or limitations in the design, implementation or analysis of a review could bias the results. Therefore, it is necessary to critically appraisal the SRs or meta-analysis to provide conclusive evidence, especially in term of methodology. ROBIS (risk of bias in systematic reviews), which was developed lately, aims mainly to assess the risk of bias in the conduct and result interpretation of systematic reviews relating to interventions, etiology, diagnosis, and prognosis.[16]

Hence, the purpose of our study was to assess the risk of bias in using ROBIS tool for SRs or meta-analysis trastuzumab-based in the treatment of breast cancer, which may provide useful advice for the methodological implementation of SRs or meta-analysis, especially in terms of safety.

2. Materials and methods

2.1. Search strategy

We searched EMBASE, PubMed, The Cochrane library, Web of science, international prospective register of systematic reviews (PROSPERO), China National Knowledge Infrastructure (CNKI), Chinese BioMedical Literature Database (CBM), Wan Fang Data and VIP database on April 11, 2019 without language limitation. The following terms were searched as Medical Subject Headings terms and free text terms: "breast cancer", "breast neoplasm", "breast tumor", "mammary neoplasms", "Herceptin", and "trastuzumab", "systematic review/meta-analysis". The detailed retrieval strategy is available in Supplementary file Table 1, http://links.lww.com/MD/F575, taking PubMed as an example. In addition, the reference lists of previously captured articles were retrieved manually to increase the possibility of finding relevant systematic reviews.

2.2. Selection of systematic reviews

The records obtained from the retrieval database, including titles and abstracts of the reviews, were downloaded and exported to EndNote database (Version X8). First, duplicates were identified and deleted from the bibliographic records. Then, 2 reviewers (Hua Wei and Yongjun Zhang) screened eligible SRs dependently according to the following inclusion criteria:

1. compared breast cancer patients treated with and without trastuzumab,
2. was fully full text,
3. was published in English or Chinese, and
4. was a systematic reviews or meta-analysis;

   Exclusion criteria:

1. treatment with HER2 targeted agents other than trastuzumab, alone or in combination with trastuzumab,
2. articles abstract and letter,
3. narrative review, screened the titles and abstracts of the unique records.

Subsequently, available full-text of the remaining papers were searched, perused, and evaluated according to the inclusion and exclusion criteria by Hua Wei and Yongjun Zhang. Disagreements were resolved by discussion, if necessary, the third person involved in judgment.

2.3. Assessment of methodological quality

Two authors assessed the methodological quality of SRs or meta-analysis by using ROBIS independently. Each reviewer recorded the results of evaluation in a predesigned excel from. If there was a discrepancy, disagreements were solved by face-to-face discussion, and the third researcher (Qian Jiang) did further assessment. The tool of Risk of Bias in Systematic Review (ROBIS) was completed in 3 phases:

1. assess relevance (optional),
2. identify concerns with the review process and
3. judge risk of bias in the review, which was detailed in http://www.bristol.ac.uk/population-health-sciences/projects/robis/.

In phase 1, assessors finished the PICO (participants, interventions, comparisons, and outcomes) for the systematic review to be evaluated using ROBIS, and were then answered whether the 2 questions (target question and systematic review question) match. If 1 or more of the PICO do not match, then this should be rated as "No". If there is a partial match between categories, then this should be rated as "partial". Phase 2 aims to identify areas where bias may be introduced into the SRs/meta-analysis. It involves 4 domains with 21 relating signaling questions and a summary judgment of risk of bias for each domain, including: study eligibility criteria; identification, and selection of studies; data collection and study appraisal; and synthesis and findings. Phase 3

aims to assess the risk of bias of the whole systematic review with 3 signaling questions. All of the signaling questions are answered as "Yes", "Probably Yes", "Probably No", "No" and "No Information", with "Yes" indicating low concerns. The subsequent level of concern about bias associated with each domain is then judged as "low", "high", or "unclear". If the answers of all signaling questions for each domain are "yes" or "probably yes", then level of concern can be judged as low. If any signaling question is answered "no" or "probably no", potential for concern about bias exists. However, the "no information" used only when insufficient data are reported to permit a judgment.

2.4. Date extraction

Data from the included systematic reviews were extracted using pre-designed extraction forms and 2 reviewers completed it independently. If the differences cannot be resolved through discussion, the third reviewer (Xiaoyan Yan) will be consulted and the fourth reviewer will check all the data. All information that were extracted from systematic reviews included the following: the journal name, the first author's name, publication date, country, searching database, searching terms, language and time limitation, additional retrieval, study design, treatment regimens, primary outcomes, major findings, numbers of reviewers for screening for eligible study, extraction data and quality evaluation, methodological evaluation tool, whether retrieve registration platform,

whether the review was registered or protocol published, whether to prove the stability of the results, whether the reporting followed the PRISMA checklist. In order to reduce the deviation in this process, our research strictly follows our predesign scheme.

3. Results

3.1. Systematic review search and screening results

The literature search yielded 1314 records and Figure 1 depicts the detailed screening process of articles included in our systematic review. From this initial records, 273 duplicates were identified and excluded. After perusing the titles and abstracts of review, 939 studies were rejected because they did not meet the criteria. Therefore, the full texts of the remaining 102 citations were retrieved for further evaluation. Seventy nine publications were excluded for the following reasons: 38 were noncompliance with inclusion and exclusion criteria, 17 were abstract or letter, 4 were narrative review, 7 was a SR protocol, 4 could not get the full review, and 9 were duplicate publications. In the end, this review was composed of 23 systematic reviews.

3.2. Characteristics of the included study

The basic characteristics of included SRs or meta-analysis were summarized in the Table 1. The included SRs or meta-analysis were published between 2006 and 2018, 18 were published in
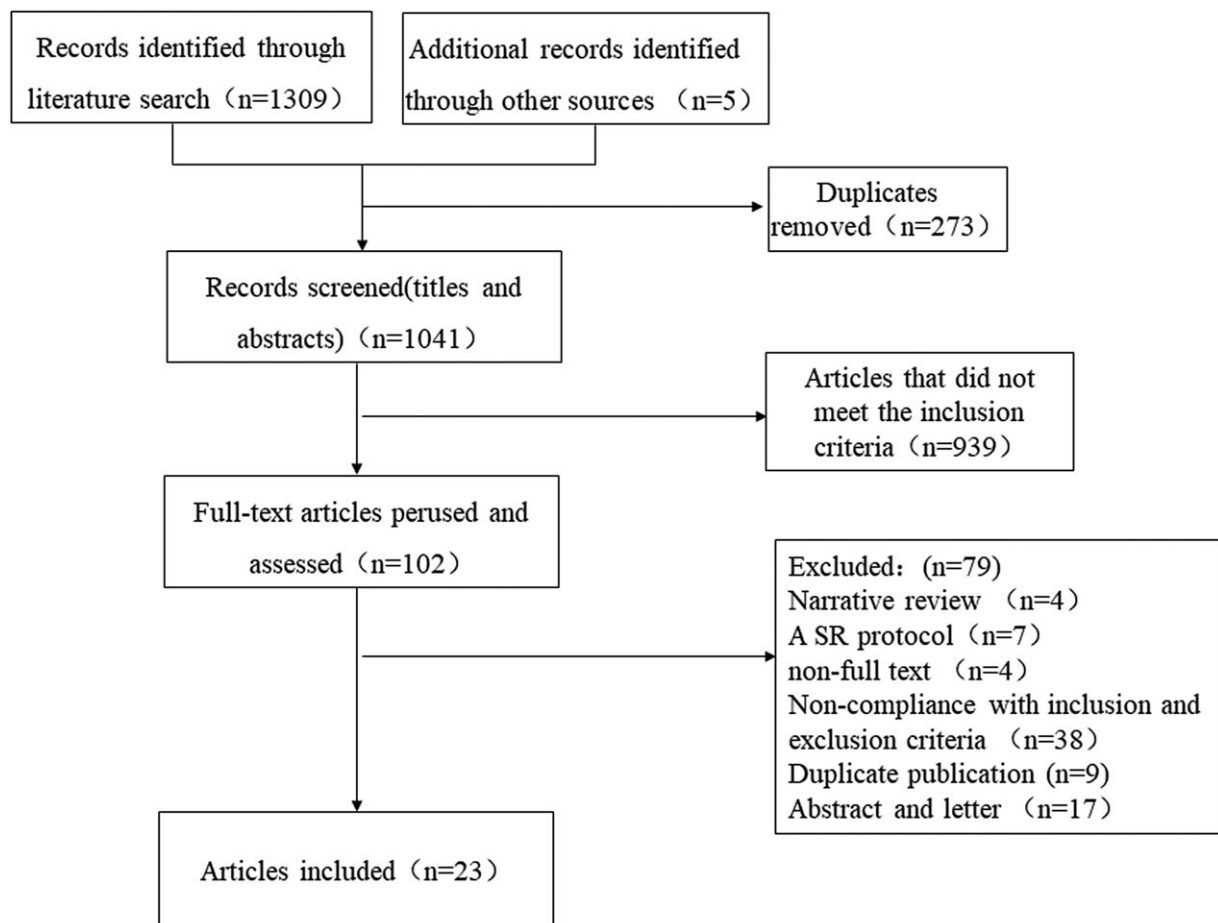

Figure 1. Flow diagram of systematic reviews election.

English and 5 in Chinese,[14,17–20] 2 of them were Cochrane reviews[21,22] and 1 of them was a network meta-analysis.[23] About 43% SRs or meta-analysis were completed by in China, 26% were completed by in Italy, respectively. In term of searching databases, 14 (61%) and 9 (39%) SRs or meta-analysis searched PubMed and the Cochrane, respectively, 7 (30%) SRs or meta-analysis searched EMBASE, MEDLINE, respectively, 3 SRs or meta-analysis searched Chinese databases containing CBM, CNKI, VIP, Wan fang database, and so on. On whether to confirm the relevant research through additional retrieval, more than half SRs or meta-analysis did through references from the retrieved articles and previous SRs manually, 13 (56%) SRs or meta-analysis searched the major international congresses' proceedings. But resources (Supplemental Table 2, http://links.lww.com/MD/F576).[33]

During the screening, data extraction and risk of bias assessment process, only 7 (30%) SRs or meta-analysis described the two-reviewers model in the screening for eligible original articles, 14 (61%) SRs or meta-analysis described the 2 reviewers to extract data, and 6 (26%) SRs or meta-analysis described the 2 reviewers to assess risk of bias. The specific methodological evaluation tool was described in 12 (52%) SRs or meta-analysis, including the Jadad scoring and Cochrane reviewer' handbook. As far as whether followed the PRISMA checklist in the reporting of the results, 18 (78%) studies provided full electronic search strategy for at least 1 database, 11 (47%) studies not reported methods used for assessing risk of bias of individual studies and 2 studies not reported electronic search resource (Supplemental Table 3, http://links.lww.com/MD/F577).

3.3. Assessment of methodological quality

The assessment risk of bias of all systematic reviews was conducted in 3 phases. The methodological quality assessment was independently completed by 2 reviewers using ROBIS tools, and solved through face-to-face discussion, if necessarily the third review (Qian Jiang) did further assessment. We presented the final risk of bias assessment results of each system review through the following tables and explanations.

3.4. Phase 1: assessing relevance (optional)

In phase 1, in terms of the PICO, all the SRs or meta-analysis were assessed whether the target question and systematic review question matched. About 85% were rated as "yes" and 15% rated as "partial", which indicated that the research question was well related to the SR. Previous to the execution of SRs, all authors have been proficient in the research dynamic and illuminated the objective clearly (Supplemental Table 4, http://links.lww.com/MD/F578).

3.5. Phase 2: identifying concerns with the review process

The first domain concerns study eligibility criteria, which was assessed whether pre-specified, clear and appropriate to the review question, 5 signaling questions were assessed in each SR or meta-analysis. All of them were rated as "yes" or "probably yes" based on the appropriateness and clarity of the study eligibility criteria. Seven studies" research source was restricted public published or published in English, which rated as "probably no" in eligibility criteria based on sources of information appropriately. Fifteen (65%) SRs or meta-analysis were rated as "low" in

this domain of bias judgment, 7 (35%) SRs or meta-analysis were rated as "high", which indicated that eligibility criteria of some the original studies might not appropriate for the issue to be settled SRs or meta-analysis (Table 2 for details).

A total of 5 signaling questions related to the identification and selection of research methods in domain 2 were evaluated to assess whether any origin studies that that have satisfied the inclusion criteria were not included in the review. With regards to searching databases or electronic sources, no non-Cochrane systematic review has done this work fully and properly in terms of comprehensive access to published and unpublished research. Only 9 SRs or meta-analysis searched the clinical trials registry platform, which included Cochrane Central Register of Controlled Trials and Clinical Trials. Fifteen studies (65%) reported additional methods in addition to database retrieval to identify possible relevant reports. A qualified retrieval resource should include the MEDLINE, EMBASE, conference report and registry platform at least and should include all published and unpublished literature. Eight SRs did report combine Mesh items with key words, and only 4 SRs provided detailed search strategy. To ensure the retrieval strategy of development searched as many eligible studies as possible, the use of filters and other limits (language or time) should be appropriate. Only 7 (30%) SRs or meta-analysis did make efforts to minimize error in selection of studies by least 2 reviewers, and 9 studies not reported relate information. Based on the result of assessment of signaling questions, high risk existed in all the non-Cochrane SRs or meta-analysis with poor conduction (Table 3 for details).

Five signaling questions in domain third were rated in each SR or meta-analysis, the main purpose of which was to determine whether bias may have been introduced in the process of data collection and risk of bias assessment. For data collection, 14 (61%) SRs or meta-analysis did try to minimize errors in data collection of studies by least 2 authors. The primary study characteristics were adequately detailed in all SRs or meta-analysis so that both review authors and readers to be able to interpret the results, and data extraction of studies results was appropriately in all SRs or meta-analysis. For methodology quality appraisement, only about 35% SRs or meta-analysis did the assessment of methodological quality using the Cochrane Reviewer handbook and 4 (17%) studies using the Jadad scoring, respectively. However, only 6 (26%) of them completed methodology quality evaluation by 2 authors. Although SRs or meta-analysis used Jadad scoring, all of them without alone assessed allocation concealment. Eventually, 7 (30%) SRs or meta-analysis were evaluated as "Low" risk of bias and 70% as "high" risk of bias, which showed inferior conduction of data collection and study appraisal (Table 4 for details).

Domain 4 concerns the synthesis and findings, which were rated whether used appropriate methods to combine data, 6 signaling questions were assessed in each SR or meta-analysis. All of SRs or meta-analysis data synthesis contain all the research that should be included. Only 2 Cochrane SRs had a protocol, and the remaining could not be identified whether the eligibility criteria or data extraction table or statistical method were determined in advance and all of them were followed or not. About a half of them did draw the funnel plot or Begg or Egger test to judge whether the publication bias existed or not. To minimize the study variation, all of SRs or meta-analysis was evaluated the heterogeneity using the I-squared (I^2) and Chi-Squared (χ^2) tests and 14 SRs or meta-analysis conducted subgroup analysis or sensitivity analyses to ensure the stability of

Table 1

Characteristics of the included studies.

Published year	Author	No. of included studies	No. of Patients	Object	Research description			Limitations of inclusion studies				Major findings
					Design	Setting	Research theme	Language	Published status	Follow-up time	Age	
2018	Shen et al[23]	9	19124	Early stage BC	RCTs	adjuvant	Efficacy of adjuvant trastuzumab-containing chemotherapies	NR	NR	NR	NR	Concurrent H with ACT or TC showed most clinical benefit for early-stage HER2+ BC; TC+H had lowest cardiotoxicity.
2017	Li et al[17]	6	18604	BC	phase III RCTs	neoadjuvant	Cardiotoxicity of trastuzumab	NR	NR	NR	≥18years	Trastuzumab therapy increases the incidence of cardiotoxicity above grade II and III, but does not increase the incidence of cardiogenic death.
	Davari et al[24]	11	20924	early stage BC	RCTs	adjuvant	Effectiveness of trastuzumab as adjuvant therapy	NR	NR	NR	NR	The addition of trastuzumab as adjuvant therapy in early stages of BC in HER2 positive patients could increase OS and DFS of the patients effectively.
2016	Chen et al[25]	13	14546	BC	RCTs	adjuvant	Efficacy, safety and administration timing of trastuzumab	NR	NR	≥1year	NR	Treatment with trastuzumab and chemotherapy improved disease-free survival, overall survival and overall response. a higher incidence of neutropenia leukopenia diarrhea, left ventricular ejection fraction reduction and congestive heart failure. The incidence of mortality and cardiac toxicity following concurrent and weekly use of trastuzumab was significantly lower compared to treatment with trastuzumab sequentially and every 3 weeks.
2015	Leung et al[26]	7	116702	BC	RCTs and cohort studies	adjuvant	Trastuzumab-induced cardiotoxicity	English	NR	NR	aged 60 years or older	Trastuzumab is likely associated with an increased risk of cardiac toxicity in elderly patients with HER2-positive breast cancer.
	O'Sullivan et al[27]	4	4220	Early BC and Tumors≤ 2 cm	RCTs	adjuvant	Efficacy of Adjuvant Trastuzumab	NR	NR	NR	NR	Women with HER2-positive tumors 2cm in the randomized trastuzumab trials derived substantial DFS and OS benefit from adjuvant trastuzumab.
	Liu et al[19]	4	9593	Early stage BC	RCTs	adjuvant	Efficacy and Safety of Trastuzumab in Adjuvant Therapy	NR	published	NR	NR	Trastuzumab combined with chemotherapy was significantly more effective than chemotherapy alone in treating HER2-positive breast cancer, but there was also a significant increase in cardiac events.
2014	Balduzzi et al[22]	7	1497	metastatic BC	RCTs	adjuvant	Trastuzumab-containing regimens for metastatic breast cancer	NR	NR	NR	any age	Trastuzumab improved overall survival and progression-free survival in HER2-positive women with metastatic breast cancer, but it also increased the risk of cardiac toxicities, such as congestive heart failure and LVEF decline.
2013	Brollo et al[28]	5	1084	BC	RCTs	adjuvant	Adjuvant trastuzumab in elderly	English	NR	NR	≥60years	Compared with chemotherapy alone, 47% relative risk reduction was observed in trastuzumab group. Proportion of cardiac events in older patients treated with trastuzumab was 5%.
	Zhu et al[29]	5	1043	metastatic or advanced BC	RCTs	adjuvant	Efficacy and Safety of Trastuzumab Added to Standard Treatments	English	NR	NR	NR	The addition of trastuzumab to chemotherapy improved OS, while to hormone therapy did not. All trastuzumab–containing regimens increased cardiac toxicity and grade 3–4 AEs.
	Zhang et al[20]	6	1062	metastatic or advanced BC	RCTs	adjuvant	Trastuzumab Plus Adjuvant Chemotherapy	NR	published	NR	NR	There was no significant difference in the pathological complete response rate between adjuvant chemotherapy combined with trastuzumab and standard. therapy, significant difference in response rate between adjuvant chemotherapy combined with trastuzumab and standard therapy.
	Olson et al[30]	4	9020	BC	phase II or phase III RCTs	adjuvant	Incidence and risk of central nervous system metastases as site of first recurrence	English	NR	NR	NR	Adjuvant trastuzumab was associated with a significant increased risk of CNS metastes as the site of first recurrence in BC patients.
2012	Moja et al[21]	8	11991	Early and locally advanced stage BC	RCTs	adjuvant	Trastuzumab containing regimens for early breast cancer	NR	NR	NR	any age	Adjuvant trastuzumab improved survival with increased risk of cardiac toxicity. Also, studies with concurrent administration showed similar efficacy and toxicity results to sequential studies.
	Valachis et al[15]	5	515	BC	RCTs	neoadjuvant	Trastuzumab combined to neoadjuvant chemotherapy	NR	NR	NR	NR	The probability to achieve pCR was higher for trastuzumab group. No significant difference in terms of CNS rate. The addition of trastuzumab did not increase the incidence of neutropenia, neutropenic fever, and cardiac AEs.

Table 1

(continued).

Published year	Author	No. of included studies	No. of Patients	Research description				Limitations of inclusion studies				Major findings
				Object	Design	Setting	Research theme	Language	Published status	Follow-up time	Age	
2011	Chen et al[31]	10	11882	BC	phase II and III RCTs	(neo) adjuvant	Risk of cardiac dysfunction with trastuzumab	NR	NR	NR	NR	Anti-HER2 antibody trastuzumab is associated with a significantly increased risk of CHF and LVEF decrease in patients with breast cancer.
	Petrelli et al[32]	2	277	BC	RCTs	neoadjuvant	Neoadjuvant chemotherapy and concomitant trastuzumab	NR	NR	NR	NR	Trastuzumab should be given to patients with HER2-positive locally advanced and inflammatory BC (and maybe early BC) together with neoadjuvant chemotherapy, even with anthracycline based, without concern for cardiac safety.
	Petrelli et al[33]	6	13331	Early stage BC	phase III RCTs	adjuvant	Concomitant compared to sequential adjuvant trastuzumab in breast cancer	NR	NR	NR	NR	In concomitant analysis, DFS and OS were longer, but risk of severe cardiac events had no increased in the trastuzumab group; In sequential analysis, DFS was longer but not OS, risk of severe cardiac events was increased in trastuzumab group.
	Yin et al[34]	6	12877	Early stage BC	RCTs	adjuvant	Trastuzumab in the Adjuvant Treatment of HER2-Positive Early Breast Cancer Patients	English	NR	NR	NR	Patients in trastuzumab group derived benefit in DFS, OS, locoregional and distant recurrence, but did worse in CNS recurrence. Concomitant use of trastuzumab lowered the risk of death but bore a higher CNS recurrence risk, OS and CNS recurrence had no difference between the sequential and observation groups.
2009	Liao et al[18]	3	451	operable or locally advanced infiltration BC	prospective RCTs	neoadjuvant	neoadjuvant chemotherapy combined with trastuzumab	NR	NR	NR	≥18years	Compared with chemotherapy alone, neoadjuvant chemotherapy combined with trastuzumab significantly increased the pCR rate of HER2-positive breast cancer patients without significantly increasing the incidence of cardiotoxicity.
2008	Bria et al[35]	5	1186	BC	prospective phase III RCTs	adjuvant	Cardiotoxicity and incidence of brain metastases after adjuvant trastuzumab	NR	NR	NR	NR	DFS and OS were significantly prolonged in trastuzumab group with a higher incidence of CHF, LVEF reduction and BM.
2007	Dahabreh et al[36]	5	13493	Early stage BC	RCTs	adjuvant	Trastuzumab in the Adjuvant Treatment	NR	NR	NR	NR	Superiority was observed for patients receiving trastuzumab with respect to DFS, mortality, locoregional recurrence, and distant recurrence. Patients in trastuzumab group had a higher risk for CHF, LVEF, and CNS metastasis.
	Viani et al[13]	5	9117	Early stage BC	RCTs	adjuvant	Adjuvant trastuzumab in early	NR	NR	NR	NR	Adjuvant Trastuzumab showed a significant reduction of mortality, recurrence, metastases rates and second tumors other than breast cancer as compared to no adjuvant Trastuzumab patients. more grade III or IV cardiac toxicity after trastuzumab versus no trastuzumab.
2006	Lin et al[14]	4	9116	Early stage BC	prospective RCTs	adjuvant	Effects of Trastuzumab Plus Adjuvant Chemotherapy for the Prognosis	NR	published	≥1year	NR	Trastuzumab combined with adjuvant chemotherapy for the treatment of HER2-positive early breast cancer can significantly improve the disease-free survival rate of patients and reduce the distant recurrence rate, but there is no significant improvement in the overall survival rate, and it may have a cardiotoxic effect.

ACT = anthracycline with sequential or concurrent taxane, AEs = adverse events; BC = breast cancer, BM = brain metastases, CHF = congestive heart failure, CNS = central nervous system, DFS = disease-free survival, H = Trastuzumab, HER2 = human epidermal growth factor receptor 2, LVEF = left ventricular ejection fraction reduction, NR = not report, OS = overall survival , pCR = pathologically complete response, RCTs = randomized controlled trials, TC+H = docetaxel and carboplatin (TC) with concurrent trastuzumab.

Table 2

Specification of study eligibility criteria.

Study/year	Signaling question 1	Signaling question 2	Signaling question 3	Signaling question 4	Signaling question 5	Bias associated with domain 1
Shen et al. (2018)	PY	Y	Y	Y	PY	Low
Li et al (2017)	PY	Y	Y	Y	Y	Low
Davari et al (2017)	PY	Y	Y	Y	PY	Low
Chen et al (2016)	PY	Y	Y	Y	Y	Low
Leung et al (2015)	PY	PY	Y	Y	PN	High
O'Sullivan et al (2015)	PY	Y	Y	PY	PY	Low
Liu et al (2015)	PY	PY	Y	Y	PN	High
Balduzzi et al (2014)	Y	Y	Y	Y	Y	Low
Brollo et al (2013)	PY	Y	Y	PY	PN	High
Zhu et al (2013)	PY	Y	Y	Y	PN	High
Zhang et al (2013)	PY	Y	Y	Y	PN	High
Olson et al (2013)	PY	PY	Y	Y	PN	High
Moja et al (2012)	Y	Y	Y	Y	Y	Low
Petrelli et al. (2012)	PY	PY	PY	Y	PY	Low
Chen et al (2011)	PY	PY	Y	Y	Y	Low
Petrelli et al (2011)	PY	PY	Y	Y	Y	Low
Valachis et al (2011)	PY	Y	Y	Y	PY	Low
Yin et al (2011)	PY	Y	Y	Y	PY	Low
Liao et al. (2009)	PY	PY	Y	Y	PY	Low
Bria et al (2008)	PY	PY	Y	PY	PY	Low
Dahabreh et al (2008)	PY	Y	Y	PY	PY	Low
Viani et al (2007)	PY	Y	Y	Y	PY	Low
Lin et al (2006)	PY	Y	Y	PY	PN	High

N = no, NI = no information, PN = probably no, PY = probably yes, Y = yes.

the results. Seven SRs or meta-analysis were minimal biases in primary studies or addressed the biases in the synthesis, and 11 SRs or meta-analysis could not be judged by the absence of the methodological quality evaluation. Based on the above 6 signaling questions, 4 SRs or meta-analysis were evaluated as "low" risk of bias and 19 as "high" risk of bias, which also indicated inferior conduction of the systematic review (Table 5 for details).

Table 3

Identification and/or selection of studies.

Study	Signaling question 1	Signaling question 2	Signaling question 3	Signaling question 4	Signaling question 5	Bias associated with domain 2
Shen et al (2018)	N	N	YN	Y	YN	High
Li et al (2017)	YN	N	PY	Y	Y	High
Davari et al (2017)	YN	Y	Y	Y	Y	High
Chen et al (2016)	YN	Y	YN	Y	NI	High
Leung et al (2015)	YN	Y	YN	YN	NI	High
O'Sullivan et al (2015)	N	Y	PY	PY	NI	High
Liu et al (2015)	N	PY	N	PN	NI	High
Balduzzi et al (2014)	Y	Y	Y	Y	Y	Low
Brollo et al (2013)	N	N	PY	N	Y	High
Zhu et al (2013)	N	Y	Y	PN	Y	High
Zhang et al (2013)	N	N	PN	PN	NI	High
Olson et al. (2013)	N	N	N	PN	NI	High
Moja et al (2012)	Y	Y	Y	Y	Y	Low
Petrelli et al (2012)	NI	NI	NI	PY	NI	High
Chen et al. (2011)	N	Y	PN	Y	NI	High
Petrelli et al (2011)	N	N	PN	Y	NI	High
Valachis et al (2011)	PN	Y	PN	Y	NI	High
Yin et al (2011)	N	Y	PN	Y	Y	High
Liao et al (2009)	N	Y	PN	PY	NI	High
Bria et al (2008)	N	N	N	Y	N	High
Dahabreh et al (2008)	PN	Y	YN	Y	N	High
Viani et al (2007)	N	Y	PY	Y	Y	High
Lin et al. (2006)	Y	Y	PN	PN	N	High

N = no, NI = no information, PN = probably no, PY = probably yes, Y = yes.

Table 4

Data collection and study appraisal.

Study	Signaling question 1	Signaling question 2	Signaling question 3	Signaling question 4	Signaling question 5	Bias associated with domain 3
Shen et al (2018)	Y	Y	PY	Y	NI	Low
Li et al (2017)	Y	Y	Y	Y	Y	Low
Davari et al (2017)	NI	PY	PY	Y	NI	High
Chen et al (2016)	Y	Y	Y	Y	Y	Low
Leung et al (2015)	Y	PY	PY	Y	NI	Low
O'Sullivan et al (2015)	NI	PY	PY	NI	NI	High
Liu et al (2015)	NI	PY	Y	PN	NI	High
Balduzzi et al (2014)	Y	PY	PY	Y	Y	Low
Brollo et al (2013)	NI	PY	PY	NI	NI	High
Zhu et al. (2013)	Y	PY	PY	Y	Y	Low
Zhang et al (2013)	NI	PY	PY	PN	NI	High
Olson et al (2013)	Y	Y	PY	NI	NI	High
Moja et al (2012)	Y	PY	Y	Y	Y	Low
Petrelli et al (2012)	NI	Y	PY	NI	NI	High
Chen et al (2011)	Y	Y	PY	PN	NI	High
Petrelli et al (2011)	NI	Y	PY	NI	NI	High
Valachis et al (2011)	Y	PY	PY	NI	NI	High
Yin et al. (2011)	Y	Y	PY	NI	NI	High
Liao et al (2009)	Y	PY	PY	PN	Y	High
Bria et al (2008)	Y	PY	PY	NI	NI	High
Dahabreh et al (2008)	Y	PY	PY	NI	NI	High
Viani et al (2007)	Y	Y	PY	PN	PY	High
Lin et al (2006)	N	PY	PY	NI	NI	High

N = no, NI = no information, PN = probably no, PY = probably yes, Y = yes.

3.6. Phase 3: judging risk of bias

The final phase involves 3 signaling question to assess whether the interpretation of findings addresses all of the problems identified in domains 1 to 4, whether the relevance of inclusion in the studies was taken into account, and whether reviewers avoided emphasizing statistical significance results. Four (17%) SRs or meta-analysis addressed the identified bias in the interpretation of findings of the domain 1–4 in phase 2. The relevance of all SRs or meta-analysis to the review's research question appropriately considered, and 18 (78%) SRs or meta-analysis's result of

Table 5

Synthesis and findings.

Study	Signaling question 1	Signaling question 2	Signaling question 3	Signaling question 4	Signaling question 5	Signaling question 6	Bias associated with domain 4
Shen et al (2018)	Y	NI	PY	PY	NI	PN	High
Li et al (2017)	Y	NI	Y	Y	PY	PY	Low
Davari et al (2017)	Y	NI	Y	PY	NI	PY	High
Chen et al (2016)	Y	NI	Y	Y	Y	Y	Low
Leung et al (2015)	Y	NI	PY	PN	Y	Y	High
O'Sullivan et al (2015)	PY	NI	PY	PN	PY	NI	High
Liu et al (2015)	PY	NI	PY	Y	PY	PN	High
Balduzzi et al (2014)	PY	Y	PY	Y	Y	PY	Low
Brollo et al (2013)	PY	NI	PY	Y	NI	NI	High
Zhu et al (2013)	PY	NI	PY	PY	NI	PY	High
Zhang et al (2013)	PY	N I	PY	PN	PY	PN	High
Olson et al (2013)	Y	NI	PY	PY	Y	N	High
Moja et al (2012)	PY	Y	PY	PY	Y	PY	Low
Petrelli et al (2012)	Y	NI	Y	PY	NI	N	High
Chen et al (2011)	Y	NI	PY	PY	PY	PN	High
Petrelli et al (2011)	Y	NI	PY	PY	PN	N	High
Valachis et al (2011)	PY	NI	PY	Y	NI	PN	High
Yin et al (2011)	Y	NI	Y	Y	Y	N	High
Liao et al (2009)	PY	NI	PY	PY	NI	PN	High
Bria et al (2008)	PY	NI	PY	PY	PY	N	High
Dahabreh et al (2008)	Y	NI	PY	PY	PY	N	High
Viani et al (2007)	Y	NI	Y	Y	PY	PN	High
Lin et al (2006)	Y	NI	PY	Y	N	N	High

N = no, NI = no information, PN = probably no, PY = probably yes, Y = yes.

Table 6

Risk of bias in the review.

Study	Signaling question 1	Signaling question 2	Signaling question 3	Bias associated with Phase 3
Shen et al (2018)	N	PY	Y	High
Li et al. (2017)	PY	Y	Y	Low
Davari et al (2017)	PN	PY	Y	High
Chen et al (2016)	PY	Y	Y	Low
Leung et al (2015)	PN	PY	Y	High
O'Sullivan et al (2015)	PN	PY	Y	High
Liu et al (2015)	PN	PY	Y	High
Balduzzi et al (2014)	Y	Y	Y	Low
Brollo et al (2013)	N	PY	PN	High
Zhu et al (2013)	N	PY	PN	High
Zhang et al (2013)	PN	Y	Y	High
Olson et al (2013)	PN	Y	PN	High
Moja et al (2012)	Y	Y	Y	Low
Petrelli et al (2012)	N	Y	PY	High
Chen et al (2011)	PN	PY	Y	High
Petrelli et al (2011)	N	PY	PN	High
Valachis et al (2011)	PN	PY	Y	High
Yin et al. (2011)	PN	Y	PN	High
Liao et al (2009)	N	PY	Y	High
Bria et al (2008)	N	PY	Y	High
Dahabreh et al (2008)	N	PY	Y	High
Viani et al (2007)	PN	Y	Y	High
Lin et al (2006)	N	PY	Y	High

N = no; NI = no information; PN = probably no; PY = probably yes; Y = yes.

statistical significance or nonstatistical significance were explained definitely in the results and discussions. Finally, 4 SRs or meta-analysis were evaluated as "low" risk of bias and 19 as "high" risk of bias, which also showed 82% of SRs were accomplished with high risk of bias (Table 6 for details).

4. Discussion

This review focused on the methodological quality of systematic reviews or meta-analysis of trastuzumab-based therapy for breast cancer, and was the first study to assess the methodological quality of SRs or meta-analysis of trastuzumab-based therapy for breast cancer by ROBIS. Among the results of the study, 35% of SRs or meta-analysis existed high risk bias in establishing study eligibility criteria, high risk existed in all the non-Cochrane SRs or meta-analysis regarding methods used to identify and/or select studies, more than half SRs or meta-analysis existed high risk bias in data collection and study appraisal, and nearly 83% SRs or meta-analysis had a high risk bias in terms of synthesis and findings. In the third phase, about 83% of SRs were completed with high risk of bias.

If the results of the systematic reviews were based on all available evidence, then they were more likely to draw valid conclusions. Relying solely on evidence published in English was likely to a decrease in accuracy and may lead to a loss of subsequent validity. Trials published in English or non-English languages should be included in the systematic reviews performed. If trials published in other languages are excluded from systematic reviews, the facts and justifications for the action should be given in the paper.[37] In our study, 5 systematic reviews were included only in the studies published in English language.[26,28–30,34] Researchers should make efforts to minimize errors in selection of studies, data extraction, methodological quality evaluation. After the publication of the PRSIMA report specification in 2009, there was still a

lack of methodological evaluation of original studies with formal quality evaluation tools. The results of SRs/meta-analysis were affected by the quality of the primary studies included, methodologically, poor studies tend to exaggerate the overall estimate of therapeutic efficacy and may lead to incorrect inferences.[38] Our study found that Petrelli and Valachis published SRs of the same study design and subject in 2011, but they included 3 different numbers of original studies. Shen published in 2018 and Davari published in 2017, which included 9 and 11 original studies, respectively. We speculated that the phenomenon may relates to comprehensiveness of retrieving resource. Du et al[39] pointed out concurrent trastuzumab and anthracycline-containing chemotherapy substantially increases the risk of cardiac adverse events, and other studies deem without significantly increase of the cardiotoxicity,[32,40,41] we thought that this may be related to poor methodological quality. For adverse reactions, randomized controlled trials or systematic reviews only regard them as secondary results, and due to the limitation of observation time and sample size, it is difficult to provide definite evidence for long-term and delayed adverse reactions. Although the intensity of the observational study is not as strong as the former 2, it is feasible and is an important source of evidence for adverse reactions. For the methodology of assessment, our team focused on the cardiotoxicity of trastuzumab, and for the SRs/meta-analysis of cardiotoxicity of trastuzumab, only Leung research included randomized controlled trials and observational studies, but the study population limit for patients over the age of 60, and only in 2 RCTs and 3 cohort,[26] included in the research was not comprehensive, so the evidence insufficient applicability.

The Cochrane Library and PROSPERO website provided registration platforms for the Cochrane SR and non-Cochrane SR, respectively. If the production systematic review was issued without prior registration or provision of a protocol, which might increase the implementation bias and reduce the reliability of the

conclusions. Therefore, registration of systematic reviews was a very important step, and registration might reduce the bias in the production process.

Like all systematic reviews, ours review also has the following shortcomings and limitations. First of all, very few of the systematic reviews or meta-analysis showed compliance with the PRISMA checklist reporting guidelines in the 23 SRs we investigated. Inadequate quality of the reporting of SRs/meta-analysis is a key factor impacting our quality evaluation of the methodology to some extent. Secondly, only 2 reviewers participated in the methodology quality evaluation, which might induce bias in judgment answers. Lastly, only the published systematic reviews were searched and may miss the unpublished literature, which not conducted methodology rating, so there was a certain publication bias.

In conclusion, our study results expounded poor execution bias in the methodological quality of SRs or meta-analysis for assessing trastuzumab-based therapy for breast cancer, such as no registration or published the protocol beforehand, no retrieval registration platform and additional manual retrieval of potential eligible studies, no assessment of the methodological quality of the original research, no minimization errors in the screening of eligible studies, data extraction and methodological quality evaluation, and so on. For systematic reviews or meta-analysis of adverse reactions, we recommend the inclusion of observational studies. Researchers should registration or publishing the protocol and the reporting followed the PRISMA checklist are recommended in future research, which may control and enhance methodological quality during the process of making the systematic reviews or meta-analysis.

Acknowledgments

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