Shenqi Fuzheng Injection in the Treatment of Breast Cancer: A Meta-analysis of Randomized Controlled Trials

Shuyu Liu, MM¹, Dan Zhang, MM¹, Jiarui Wu, MD, PhD¹, Kairuan Wang, MM¹, Yi Zhao, MD, PhD¹, Mengwei Ni, MM¹, Ziqi Meng, MM¹, and Xiaomeng Zhang, MD¹

Abstract
Objective: This meta-analysis synthesized the available evidence on the effectiveness and safety of Shenqi Fuzheng injection (SQFZI) combined with chemotherapy for breast cancer. Method: A comprehensive systematic literature search was conducted to identify the randomized controlled trials (RCTs) on breast cancer treated by SQFZI in several electronic database up to October 29, 2017. The included RCTs were assessed using the Cochrane Collaboration tool; data were extracted and analyzed via RevMan 5.3 and Stata 13.0 software. Results: A total of 31 eligible RCTs comprising 2543 participants were selected in this present meta-analysis. The results demonstrated that compared with receiving conventional chemotherapy alone, SQFZI treatment combined with chemotherapy was more efficient in improving clinical total effective rate (relative risk [RR] = 1.31, 95% CI 1.19-1.44, \(P < .00001\)) and performance status (RR = 2.23, 95% CI 1.98-2.56, \(P < .00001\)). Additionally, SQFZI combined with chemotherapy was capable of enhancing immune function and alleviating adverse drug reactions for patients with breast cancer. Conclusions: The current evidence suggested that using SQFZI as an adjunct treatment to chemotherapy may be preferable for patients with breast cancer compared to chemotherapy alone. Because of the limitations of the quantities and qualities of included RCTs, more well-designed RCTs are needed to further support our conclusion.

Keywords
Shenqi Fuzheng injection, chemotherapy, breast cancer, randomized controlled trials, meta-analysis

Submitted July 31, 2018; revised November 2, 2018; accepted November 9, 2018

Introduction
Breast cancer is one of the most frequently diagnosed cancers and the leading cause of cancer death in females worldwide, accounting for 23% (1.38 million) of the total new cancer cases and 14% (458 400) of the total cancer deaths in 2008.¹⁻³ As in most other countries, breast cancer is by far the most common cancer in women in China and has posed a formidable potential threat to public health owing to its high morbidity and mortality.⁴⁻⁶ Important risk factors associated with breast cancer include estrogen receptor, progesterone receptor, growth factors, and others.⁷ Despite the remarkable advances achieved in the fields of surgery, endocrine therapy, chemotherapy, radiotherapy, and targeted therapy against breast cancer over the past several decades, most cases are still suffering from the metastasis, recurrence, and adverse drug reactions (ADRs).⁸

As an important part of complementary and alternative medicine, traditional Chinese medicine (TCM) has become one of the main methods for comprehensive anticancer treatment owing to its advantages in treating complications, preventing drug resistance, and so on.⁹ According to TCM theory, the basic pathogenesis of breast cancer is the meridian barrier, phlegm retention, qi stagnation, and blood stasis.¹⁰ Therefore, the therapeutic principle is to nourish liver and kidney, strengthen body resistance, and...
eliminate pathogen. As a new formulation of TCM, Chinese herbal injections (CHIs) own the features of notable curative efficiency and high bioavailability. Among the variety of CHIs, SQFZI has long been extensively used in the clinical setting. It is composed of Codonopsis pilosula (Franch) Nannf and Astragalus membranaceus (Fisch) Bunge and was approved by the State Food and Drug Administration of the People’s Republic of China (CFDA) in 1999. It possesses the effects of nourishing the spleen and stomach, promoting blood circulation, and removing blood stasis. Modern research has revealed that SQFZI has the characteristics of enhancing efficacy and reducing toxicity. SQFZI combined with chemotherapy is currently widely applied for treating breast cancer in China. Considering that a relevant systematic review remains lacking, we intended to investigate the efficacy and safety of SQFZI for breast cancer using meta-analysis to provide valuable evidence for clinical decision making.

**Material and Methods**

**Inclusion and Exclusion Criteria**

The inclusion and exclusion criteria were prespecified according to the PICOS (patients, intervention, comparator, outcomes, study design) criteria through discussion by the authors. Only randomized controlled trials (RCTs) meeting the following criteria were included in this meta-analysis: (1) Types of studies: RCTs focused on the effect of SQFZI combined with chemotherapy for the treatment of breast cancer. (2) Participants: all the involved participants were diagnosed as breast cancer according to the pathological, cytological, and histological features. (3) Interventions: the interventions of the control group included conventional chemotherapy agents such as cyclophosphamide, doxorubicin, epirubicin, pirarubicin, 5-fluourouracil, paclitaxel, docetaxel, methotrexate, Changchun ruisabine, gemcitabine, capetcitabine, cisplatin, mitomycin, and so forth. The experimental group included studies of SQFZI combined with the same chemotherapeutic drugs as the control group. (4) Outcomes: The primary outcomes of the research included the clinical total effective rate and the performance status. According to the therapeutic effect criterion of the World Health Organization for solid tumors, the clinical total effective rate was calculated by the following formula: (number of complete response patients + number of partial response patients)/total number of patients × 100%. Karnofsky performance status (KPS) was used to assess the performance status of patients. An increase of more than 10 points after treatment was deemed as significant improvement. Additionally, the incidence of immune functions changes (T lymphocyte subsets such as CD3+, CD4+, CD8+, CD4+/CD8+, NK cell, and peripheral hemogram) and ADRs (leukopenia, nausea and vomiting, hepatorenal dysfunction, and so on) were evaluated as secondary outcomes. The criterion of the ADRs met the World Health Organization criteria for common toxicity of chemotherapy drugs released in 1981.

Exclusion criteria were as follows: (1) Types of studies: RCTs for which full-text versions were unavailable, case reports, animal experiments, editorials, letters, and review articles; as for any publications shared overlapping information, the more recent and comprehensive article was included. (2) Interventions: The chemotherapeutic drugs, dose, and duration of treatment was incomplete or incorrect. (3) Outcomes: RCTs did not report the data of clinical total effective rate, performance status, and ADRs.

**Literature Search**

A systematic literature search was conducted to identify the published RCTs with SQFZI for the treatment of breast cancer. The retrieval was performed in the following databases from their inception to October 29, 2017: PubMed, the Cochrane library, Embase, China National Knowledge Infrastructure Database (CNKI), Wan-Fang Database, China Science and Technology Journal Database (VIP), and the Chinese Biomedical Literature Database (SinoMed). “Breast Neoplasm” was regarded as MeSH term. All the searching strategies were developed and adapted for each database. The search strategies of PubMed are listed as follows:

```
#1 Breast Neoplasm[MeSH Terms]
#2 Breast Cancer[Title/Abstract] OR Mammary Cancer[Title/Abstract] OR Breast Malignant Neoplasm[Title/Abstract] OR Breast Carcinoma[Title/Abstract] OR Breast Malignant Tumor[Title/Abstract] OR Human Mammary Carcinoma[Title/Abstract] OR Human Mammary Neoplasm[Title/Abstract]
#3 #1 OR #2
#4 Shenqi Fuzheng
#5 Randomized Controlled Trial[Publication Type]
#6 Controlled Clinical Trial[Publication Type]
#7 random*[All Fields]
#8 #5 OR #6 OR #7
#9 #3 AND #4 AND #8
```

**Data Extraction and Quality Assessment**

Two independent reviewers performed the data extraction and in case of discrepancies, a third reviewer would be consulted. The following contents were considered in data extraction: (1) baseline characteristics of included RCTs—the first author, publication date; (2) characteristics of patients—the number of patients in the experimental group and the control group, age, TNM stage; (3) details of intervention—the names, dosages, and treatment cycles of
SQFZI; and (4) outcomes—the measured data about clinical total effective rate, performance status, ADRs and immune function. All literature was managed by NoteExpress (Wuhan University Library, Wuhan, China).

Methodological quality assessment of each RCT was conducted by the Cochrane risk of bias tool (Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0). disagreements were resolved by methodological experts to reach consensus. Besides, 5 domains of bias that are relevant to the quality of RCTs, namely random sequence generation (selection bias), allocation concealment (selection bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other bias were considered.

If any RCTs described a correct random generation, or implemented blinding or reported complete measure outcomes, this RCT belonged to “low risk.” Otherwise, trials were judged as “high risk.” The evaluation of “Unclear” meant that the literature did not provide enough information for judgments.

**Statistical Analysis**

This current meta-analysis pooled data from clinical trials via Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). Dichotomous outcomes were presented as relative risk (RR), whereas continuous variable was evaluated by mean difference, and 95% confidence intervals (95% CIs) of outcomes were calculated to indicate the range of results.

The chi-square test was applied to evaluate heterogeneity among studies, and I² was used to show the magnitude of this heterogeneity. Results of $P \geq .1$ and $I^2 \leq 50\%$ suggested a lack of significant heterogeneity; the fixed-effect model was used accordingly. For cases with $P < .1$ and $I^2 > 50\%$, we adopted a random-effect model, and subgroup analysis was presented to explore the sources of heterogeneity. Meanwhile, the visual inspection of publication bias was demonstrated by funnel plot. Egger’s test and Begg’s test were also adopted, the result of $P > .05$ showed that there was no obvious publication bias among included studies.

In addition, sensitivity analysis was conducted in clinical total effective rate so as to test the stability of results, by excluding the RCT seriatim to resynthesize the data. Egger’s test, Begg’s test, and sensitivity analysis were estimated and processed using STATA 13.0 software (Stata Corporation, College Station, TX, USA).

**Quality Assessment**

After performing quality assessment, only 3 RCTs adopted a random number table to generate the group, 1 RCT grouped patients by the toss of a coin. Therefore, their selection bias was evaluated as “low risk.” Five RCTs grouped in congruence with the therapeutic methods or admission time, so the selection bias was remarked as “high risk.” The other 22 RCTs did not illustrate the specific method of random sequence generation, therefore their selection bias was “unclear risk.” Information on allocation concealment and blinding was not observed in the trials. Hence this study evaluated the selection bias of allocation concealment, performance bias, and detection bias as “unclear.” Moreover, none of the included RCTs assessed had incomplete data, thus the attrition bias and reporting bias were assessed as “low risk.” Additionally, none of the RCTs offered any details contributing to high risk for other bias, so this item was appraised as “unclear risk.” Graphical description about quality assessment is shown in Figure 2.

**Outcomes**

**Clinical Total Effective Rate.** Depending on use of anthracycline, all chemotherapy regimens were divided into anthracycline-based subgroup and other chemotherapeutic drugs subgroup. The former contained 3 main chemotherapies: cyclophosphamide + doxorubicin + 5-fluorouracil (CAF), cyclophosphamide + pirarubicin + 5-fluorouracil (CTF), or cyclophosphamide + epirubicin + 5-fluorouracil (CEF). We assessed the clinical total effective rate in 2 subgroups respectively. The results of subgroup analysis are as follows.

Anthracycline-based subgroup: 9 RCTs were available in this subgroup and displayed no heterogeneity
The results indicated a statistically significant difference between SQFZI group and control group; thus, in terms of clinical total effective rate, SQFZI combined with anthracycline-based chemotherapy was superior to the anthracycline-based chemotherapy alone (RR = 1.36, 95% CI 1.21-1.53, \( P < .00001 \)).

Other chemotherapeutic drugs subgroup: 4 RCTs demonstrated no evidence of heterogeneity in this subgroup, so the fixed-effect model was adopted (\( P = .12 > .1, I^2 = 48\% < 50\% \)). The results of meta-analysis presented a better impact when adding SQFZI than using other chemotherapeutic drugs alone. The difference between two groups was statistically significant (RR = 1.22, 95% CI 1.03-1.44, \( P = .02 \)).

There was no obvious interstudy heterogeneity reported among the subgroups (\( P = .31 > .1, I^2 = 4.3\% < 50\% \)), hence it is acceptable that the results derived from 2 subgroups could be amalgamated. The pooled analysis demonstrated that SQFZI group performed even better on improving clinical total effective rate than control group, which received chemotherapy alone. The difference between SQFZI group and control group was considered as statistically significant (RR = 1.31, 95% CI 1.19-1.44, \( P < .00001 \); Figure 3).

**Sensitivity Analysis and Publication Bias**

For the outcome of clinical total effective rate, a sensitivity analysis was carried out to verify the stability of result. As shown in Figure 4, since the clinical total effective rate did
not show a qualitative transform, the result of sensitive analysis was robust.

Although the results of Egger’s test ($t = 2.20$, $P = .05$) and Begg’s test ($z = .92$, $P = .360 > .05$) indicated no significant publication bias, the funnel plot on publication bias for clinical total effective rate presented modest asymmetry (Figure 5), which suggested that there might be potential publication bias among included RCTs.

### Performance Status

**Anthracine-based subgroup:** No significant heterogeneity was detected among 10 RCTs of this subgroup ($P = .24 > .1$, $I^2 = 23% < 50%)$, thus we applied the fixed-effect model.23-26,30,34-36,41,42 Compared with anthracline-based therapy alone, the SQFZI group was more effective in raising performance status ($RR = 2.29$, 95% CI 1.79-2.93, $P < .00001$); the difference between 2 groups was considered to be statistically significant.

### Table 1. The Basic Characteristics of the Included Studies.

| Study ID  | N (E/C) | Age, Years (E/C) | TNM Stage | Therapy of Experiment | Therapy of Control | Course (Days) | Outcome a |
|-----------|---------|-----------------|-----------|----------------------|-------------------|--------------|-----------|
| Qi QG 2013 | 20/26 | 52 (median age) | II-IV | SFI 250 mL + CAF | CAF | 21 | 2 |
| Ma FL 2015 | 36/36 | — | — | SFI 250 mL + CAF | CAF | 63 | 2,3,4,5 |
| Jia CF 2016 | 50/50 | 32-65 / 31-63 | — | SFI 250 mL + CAF | CAF | 21 | 6 |
| Wang W 2015 | 65/65 | 31-72 / 34-71 | — | SFI 250 mL + CAF | CAF | 63 | 6 |
| Wang DJ 2013 | 38/38 | 31-62 / 31-63 | II-III | SFI 250 mL + CAF | CAF | 63 | 6 |
| Xie F 2014 | 45/45 | 37-66 / 35-68 | — | SFI 250 mL + CAF | CAF | 63 | 6 |
| Yuan JW 2008 | 38/35 | >19 | II-III | SFI 250 mL + CAF | CAF | 20 | 6 |
| Lu MY 2010 | 58/52 | 32-69 | — | SFI 250 mL + CAF | CAF | 21 | 6 |
| Chen XC 2016 | 42/42 | 42.65 ± 8.27 / 42.63 ± 8.24 | II-IV | SFI 250 mL + CAF | CAF | 42 | 6,7,8 |
| Liu Y 2017 | 52/52 | 30-58 / 31-58 | I-III | SFI 250 mL + CAF | CAF | 63 | 6,7,8 |
| Fu YJ 2014 | 45/45 | 32-52 | II-III | SFI 250 mL + CAF | CAF | 63 | 6,7,8 |
| Liang F 2014 | 27/27 | 29-57 | — | SFI 250 mL + CTF | CTF | 42 | 6,7,8 |
| Huang ZF 2008 | 30/30 | 24-68 / 26-66 | II-IV | SFI 250 mL + CTF | CTF | 42 | 6,7,8,9 |
| Sun SH 2005 | 43/39 | 35-70 / 30-73 | I-III | SFI 250 mL + CTF | CTF | 42 | 6,7,8,9 |
| Zou TL 2006 | 32/32 | 29-65 | — | SFI 250 mL + CTF | CTF | 14 | 6,7,8,9 |
| Chen F 2007 | 34/34 | 38-64 | — | SFI 250 mL + CEF | CEF | 28 | 6 |
| Yang F 2016 | 40/40 | 25-67 / 26-65 | I-III | SFI 250 mL + CEF | CEF | 28 | 6 |
| Dai ZJ 2007 | 65/61 | 27-69 / 26-70 | II-III | SFI 250 mL + CEF | CEF | 28 | 6 |
| Wang SM 2006 | 40/32 | 45.2 ± 9.8 / 46.7 ± 10.5 | — | SFI 250 mL + CEF | CEF | 21 | 6 |
| Xiao HW 2005 | 55/53 | 43-67 | — | SFI 250 mL + CEF | CEF | 21 | 6 |
| Zhao BB 2012 | 63/47 | 30-74 / 29-75 | — | SFI 250 mL + ATC | ATC | 21 | 6 |
| Li XL 2004 | 40/35 | 56.4 / 54.2 | — | SFI 250 mL + NE | NE | 28 | 6 |
| Wu M 2012 | 36/36 | 35-69 / 36-68 | — | SFI 250 mL + CMF | CMF | 28 | 6 |
| Song ZJ 2011 | 21/25 | 32-65 / 35-61 | II-III | SFI 250 mL + CMF | CMF | 14 | 6 |
| Qiao CY 2013 | 20/20 | 40-65 | — | SFI 250 mL + ECX | ECX | 14 | 6 |
| A TK 2011 | 40/40 | 28-65 | — | SFI 250 mL + TA | TA | 21 | 6 |
| Chen JM 2010 | 90/95 | 42/45 | III-IV | SFI 250 mL + TD | TD | — | 6,7,8 |
| Wang L 2016 | 30/30 | 35-60 | — | SFI 250 mL + TC | TC | 21 | 6,7,8 |
| Nie JY 2005 | 30/30 | 37-65 / 36-70 | — | SFI 250 mL + 5-Fu + NVB | NVB + 5-Fu | 21 | 6,7,8 |
| Zhang Q 2013 | 32/32 | 32-67 | — | SFI 250 mL + GEM + DDP | GEM + DDP | 21 | 6,7,8 |
| Li YQ 2002 | 35/27 | 47.2 ± 10.8 / 46.7 ± 10.5 | — | SFI 250 mL + 5-Fu + DDP | 5-Fu + DDP + MMC | 21 | 6,7,8 |

Abbreviations: E, experimental group; C, control group; CAF, cyclophosphamide+ doxorubicin+ 5-fluorouracil; CTF, cyclophosphamide+ pirarubicin+ 5-fluorouracil; CEF, cyclophosphamide+ epirubicin + 5-fluorouracil; ATC, anthracyclines; NE, navelbine+ epirubicin; CMF, cyclophosphamide + methotretexate + 5-fluorouracil; ECX, capectabine; TA, paclitaxel + doxorubicin; TD, pirarubicin + docetaxel; TC, docetaxel + Epirubicin; NVB, navelbine; GEM, gemcitabine; DDP, cisplatin; MMC, mitomycin.

a, the clinical total effective rate; b, the performance status; c, adverse drug reactions (ADRs); d, immune function.
No visible heterogeneity was obtained between the two subgroups ($P = .55 > .1, I^2 = 0\% < 50\%$), so we merged these subgroups into one group. The result demonstrated that SQFZI group achieved better effects than the control group, which received chemotherapeutic drugs alone; the difference between the above 2 groups had statistical significance ($RR = 2.18, 95\% CI 1.82-2.62, P < .00001$; Figure 6).

**Other Outcomes**

This study made a qualitative description for immune function of patients, which was considered as secondary outcome. The pooled analysis demonstrated that SQFZI group performed better in preventing the loss of peripheral T-lymphocyte subsets (CD4+, CD4+/CD8+), NK cell, leukopenia, and platelets. However, the combination of SQFZI
and chemotherapy failed to achieve a better effect on CD3+, CD8+, and hemoglobin. More details regarding immune function were presented in Table 2.

Adverse Drug Reactions

In this meta-analysis, we mainly discussed three representative ADRs (leukopenia, nausea, and vomiting and hepatorenal dysfunction) and other ADRs to assess the curative effect of experimental group:

1. Twelve RCTs reported leukopenia. The overall results demonstrated that the combination of SQFZI and chemotherapy was more efficient in relieving leukopenia than the control group which only received

![Figure 4. Sensitivity analysis of the clinical total effective rate.](image1)

![Figure 5. Funnel plot of the clinical total effective rate.](image2)
Integrative Cancer Therapies

between-group differences were statistically significant (RR = 0.51, 95% CI 0.41-0.64, P < .00001; Figure 7a).

2. Eight RCTs covered data on nausea and vomiting: pooled results showed that SQFZI plus chemotherapy decreased nausea and vomiting compared with chemotherapy alone.27,32-34,38,45,48,52 There was no statistically significant between-group difference (RR = 0.51, 95% CI 0.40-0.66, P < .00001; Figure 7b).

3. Seven RCTs investigated hepatorenal dysfunction.24,27,28,31-33,48 The results demonstrated that the conjunctive use of SQFZI and chemotherapy can decrease the incidence of hepatorenal dysfunction observably, and no significantly statistical difference was found (RR = 0.38, 95% CI 0.25-0.59, P < .0001; Figure 7c).

Additionally, this meta-analysis demonstrated that the SQFZI group had better efficacy in relieving other ADRs caused by chemotherapeutic drugs, including electrocardiogram changes, alopecia, intestinal reaction, thrombocytopenia, hemoglobin reduction, myelosuppression, and fatigue (Table 3).

Discussion

This meta-analysis assessed the available evidences derived from 31 RCTs to detect the efficacy and safety of SQFZI combined with chemotherapy in treating breast cancer.
According to the foregoing results, SQFZI plus chemotherapy can make a nonnegligible influence versus chemotherapy alone in terms of improving clinical total effective rate and performance status. Subgroup analysis revealed that especially in improving performance status of patients, SQFZI combined with chemotherapy showed a more impressive effect. Simultaneously, this combined chemotherapy approach also enhanced immune function of breast cancer patients and relieved ADRs.

Breast cancer poses threats to the health and safety of human life. Although the treatment of this disease has been

**Table 3. Results of Other Adverse Drug Reactions (ADRs).**

| ADRs                        | N | Effect model | Relative Risk [95% CI] | P    |
|-----------------------------|---|--------------|------------------------|------|
| Electrocardiogram changes   | 5 | Fixed        | 0.27 [0.13, 0.56]      | .0004|
| Alopecia                    | 4 | Fixed        | 0.43 [0.26, 0.73]      | <.002|
| Intestinal reaction         | 3 | Fixed        | 0.49 [0.35, 0.68]      | <.0001|
| Thrombocytopenia            | 3 | Fixed        | 0.61 [0.40, 0.92]      | .02  |
| Hemoglobin reduction        | 3 | Fixed        | 0.48 [0.29, 0.78]      | .003 |
| Myelosuppression            | 2 | Fixed        | 0.56 [0.37, 0.87]      | .009 |
| Fatigue                     | 2 | Fixed        | 0.51 [0.36, 0.72]      | .0001|

According to the foregoing results, SQFZI plus chemotherapy can make a nonnegligible influence versus chemotherapy alone in terms of improving clinical total effective rate and performance status. Subgroup analysis revealed that especially in improving performance status of patients, SQFZI combined with chemotherapy showed a more impressive effect. Simultaneously, this combined chemotherapy approach also enhanced immune function of breast cancer patients and relieved ADRs.
constantly improved, ADRs of patients have still increased year by year, which becomes a significant handicap to enhancing the curative effect of breast cancer. In TCM theories, the occurrence of breast cancer is mostly associated with invasion of exopathogens and the deficiency of Qi-blood. Furthermore, research suggested thereby improving the immunosuppression caused by chemotherapeutic drugs. Additionally, research suggested that astragaloside could inhibit the proliferation of tumor cells in S phase and G2/M phase, suppress the expression of p21 and reduce the activity of cyclin-dependent kinase. The authors concluded that astragaloside could be used as an effective adjuvant chemotherapeutic drug in cancer treatment.

As one of the effective components of , , polysaccharides (CPP) could cause the inhibition of SMMC-7721 cells of hepatoma cells without obvious toxicity to viscera of Kunming mice. To summarize, these 2 kinds of Chinese herbs synergistically nourish Qi-blood, reinforce kidney and spleen, and eliminate stagnation.

Currently, there is a lack of systematic reviews comparing SQFZI combined with chemotherapy in the treatment of breast cancer. In this regard, our meta-analysis provides relevant medical evidence in this field and has the following advantages: First, to our knowledge, the present study is the first meta-analysis which delved into the efficacy and safety of SQFZI combined with chemotherapy in treating breast cancer. Second, we conducted a comprehensive literature search to identify the published studies through the combination of MeSH terms and text words. Clearer inclusion and exclusion criteria have been introduced, and the patients were diagnosed with breast cancer by a definite diagnostic standard, with a relatively consistent baseline. Third, we carried out subgroup analysis in the light of whether anthracyclines were used or not, which demonstrated that regardless of use of anthracyclines, chemotherapy drugs combined with SQFZI had superior curative effect. Arguably, no conspicuous intergroup heterogeneity was found between 2 subgroups.

However, because of the limited data available for this population, the present meta-analysis had some limitations. First, only 5 RCTs specifically described randomization method, whereas they did not make a detailed description of random sequence connation, allocation concealment, or blinding methods. Besides, most items were assessed as unclear risk, which may have therefore affected the reliability of the results. Second, though the Egger’s test and Begg’s test manifested that there was no potential publication bias in present study, the deficiency of the funnel plot’s bottom also indicated a lack of RCTs with large sample. Third, our results might have limited generalizability because all of the included RCTs were performed in China among Chinese populations; therefore, it is unclear whether the effect may change when SQFZI is used in populations of other ethnicities and in different geographical locations. Fourth, because of the original research limitation, we failed to evaluate the long-term effect of SQFZI. On account of the limitations mentioned above, we raise several suggestions: first, RCTs are supposed to be registered in advance and implemented according to CONSORT standard so as to ensure the transparency of trial process. Meanwhile, the clinical trials should pay more attention to randomization, concealment, blinding methods, and long-term follow-up to provide high-quality evidence-based medical evidence for clinical decision making. In addition, clinicians ought to strengthen monitoring of ADRs while remaining concerned on the measurement of effectiveness. It is the responsibility of the medical staff to use SQFZI as per the instruction guidelines and monitor the occurrence of ADRs.

Conclusions
In summary, this study revealed that the combination of SQFZI and chemotherapy had a better effect on treating breast cancer. However, due to the limitations of the current meta-analysis, the strength of evidence needs to be promoted by rigorously designed, multicentered, large-sample randomized double-blind controlled trials.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the National Nature Science Foundation of China (No. 81473547; No. 81673829).

References
1. Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends—an update. Cancer Epidemiol Biomarkers Prev. 2016;25:16-27.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. Cancer J Clin. 2015;65:5-29.
3. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61:69-90.
4. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016;66:115-132.
5. Fan L, Strasser-Weippl K, Li J, et al. Breast cancer in China. Lancet Oncol. 2014;15:e279-e289.
6. Zheng Y, Wu CX, Zhang ML. The epidemic and characteristics of female breast cancer in China [in Chinese]. Zhongguo Ai Zheng Za Zhi. 2013;23:561-569.
7. Dai XX, Zhang YS, Liu JH, Feng YZ. Epidemiological and clinicopathological analysis of breast cancer. Chin J Hosp Pharm. 2018;1-5. http://kns.cnki.net/kcms/detail/42.1204.R.20180211.1310.084.htm. Accessed March 11, 2018.
8. Wang CT, Li JW. Research progress on the prevention and treatment of breast cancer by traditional Chinese medicine. China Prescription Drug. 2018;2(2):18-20.
9. Zhou SY, Zhan SJ, Xu HZ, Sun DW, Tang JH. Progress of Chinese medicine in the treatment of breast cancer. Chin J Basic Med Tradit Chin Med. 2017;10(1):1489-1492.
10. Gao Y, Wang XX. Diagnosis and treatment of different stages of breast cancer from the theory of “get along with them.” J Tradit Chin Med. 2013;54:1434-1436.
11. Dong FF, Ren Q. Study on TCM syndromes and treatment of breast cancer. Chin J Ethn Ethn. 2018;(1):22-23.
12. Lai YF, Chen XP, Lu JJ, Hu H, Wang YT. Analysis of anti-neoplastic traditional Chinese medicine injections based on market conditions. Modern Tradit Chin Med Materia Medica World Sci Technol. 2012;(5):1958-1962.
13. Yang Y, Ting W, Xiao L, et al. Immunoregulation of Shenqi Fuzheng injection combined with chemotherapy in cancer patients: a systematic review and meta-analysis. Evid Based Complement Alternat Med. 2017;2017:5121538.
14. Li PW, Bi GW, Liu BK. Shenqi Fuzheng injection combined with chemotherapy in the treatment of malignant tumors. China J Chin Materia Medica. 2000;25:115-117.
15. Duffaud F, Therras P. New guidelines to evaluate the response to treatment in solid tumors [in French]. Bull Cancer. 2000;87:881-886.
16. People’s Republic of China Department of Health Management. Guidelines for the Diagnosis and Treatment of Cancer 1991. Beijing, China: Peking Union Medical College Press;11-15.
17. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
18. Review Manager (RevMan) [computer program]. Version 5.3. Copenhagen, Denmark: The Nordic Cochrane Centre; 2014.
19. Wang K, Zhan D, Wu J, Liu S, Zhan X, Zhan B. A comparative study of Danhong injection and Salvia miltiorrhiza injection in the treatment of cerebral infarction: a systematic review and meta-analysis. Medicine (Baltimore). 2017;96:e7079.
20. Salanti G, Higgins J P, Ades A E, Ioannidis JP. Evaluation of networks of randomized trials. Stat Methods Med Res. 2008;17:279-301.
21. Zhang D, Zheng J, Ni M, et al. Comparative efficacy and safety of Chinese herbal injections combined with the FOLFOX regimen for treating gastric cancer in China: a network meta-analysis. Oncotarget. 2017;8:68873-68889.
22. Tian JH, Li L, Yang KH. The realization of network meta-analysis of frequency statistics method in STATA software. Chin J Evid Based Pediatr. 2014;9:472-474.
23. Qi QG, Yue L, Wang Y, et al. Impact of Shenqi fuzheng combination chemotherapy on the expression levels of TNF-α, CCL18 and IL-6 in the serum of breast cancer patients. Chin J N Drugs. 2013;22:1196-1201.
24. Ma FL, Li XB, Yin Z, Li JM, Liu CJ. Clinical observation of Shenqi Fuzheng injection combined with chemotherapy in 36 cases of breast cancer. Pharmacol Clin Chin Materia Medica. 2015;31:109-110.
25. Jia CF, Duan M, Duan X. Effect of Shenqi Fuzheng injection combined with chemotherapy on hematopoietic function and immune function of breast cancer patients. J Hainan Med Coll. 2016;22:1866-1869.
26. Wang W. Clinical study of Shenqi Fuzheng injection combined with neoadjuvant chemotherapy in treatment of breast cancer. Chin J Chin Med. 2015;30:466-467.
27. Wang DJ. Clinical observation of Chinese and Western drugs for the treatment of 76 cases of breast cancer. Medical Recapitulate. 2013;14:2676-2678.
28. Xie F. Clinical analysis of Shenqi fuzheng injection combined with chemotherapy in the treatment of breast cancer. Guide China Med. 2014;12:19-20.
29. Yuan JW, Kong CB, Liu HF, Yang SJ. Effect of Shenqi fuzheng injection on cellular immune function in breast cancer patients undergoing neoadjuvant chemotherapy. Lishizhen Med Materia Medica Res. 2008;19:1099-1100.
30. Lu MY. The effects of Shenqi Fuzheng injection on immune function of breast cancer patients treated with CAF regimen chemotherapy. J Basic Clin Oncol. 2010;23:236-238.
31. Chen XC. The clinical effect of Shenqi Fuzheng injection combined with chemotherapy in the treatment of breast cancer. World Latest Med Inform. 2016;16:144-150.
32. Liu Y. Clinical efficacy of different drugs in treatment of breast cancer. Clin Res Pract. 2017;2:16-17.
33. Fu YJ. Clinical observation of traditional Chinese medicine and Western medicine in the treatment of breast cancer. China Pract Med. 2014;9:138-139.
34. Liang F, Zhang QS, Zhang LJ, Xing GC, Li JM. Meta-analysis of Shenqi Fuzheng injection combined with chemotherapy in the treatment of breast cancer. China Pract Med. 2014;9:175-176.
35. Huang ZF, Wei JS, Li HZ, Tan ZQ, Zhang ZJ, Chen C. Clinical observation of Shenqi Fuzheng injection combined with chemotherapy in treating 30 cases of advanced breast cancer. Chin J Integr Trad West Med. 2008;25:154-154.
36. Sun SH, Zheng XB. Application of Shenqi Fuzheng injection in postoperative chemotherapy of breast cancer. Chin J Integr Trad West Med. 2005;25:544-545.
37. Zou TL, Nie JY, Chen WL. The attenuation of Shenqi Fuzheng injection treated of advanced breast cancer patients with chemotherapy. J Pract Oncol. 2006;21:75-77.
38. Chen F, Lin H. Clinical observation of Shenqi Fuzheng injection in adjuvant chemotherapy for breast cancer. Strait Pharm J. 2007;19:75-76.
39. Yang F. Clinical significance of Shenqi Fuzheng injection in adjuvant treatment of breast cancer. Nei Mongol J Tradit Chin Med. 2016;35:65.
40. Dai ZJ, Wang XJ, Kang HF, et al. Clinical observation to the effect and adverse reaction of Shenqi Fuzheng injection in the neoadjuvant chemotherapy of breast. Adverse Drug Reactions J. 2007;9:10-14.
41. Wang SM, Guo YW, Huang GS. Application of Shenqi Fuzheng injection in adjuvant chemotherapy after breast cancer operation. Pharma Industry Inform. 2006;17(12):124.
42. Xiao HW. Shenqi fuzheng injection combined with FEC regimen in the treatment of breast cancer. J Med Theory Pract. 2005;18:885-886.
43. Zhao BB, Lei MD, Gao HW, Li JY, Wang GD. Clinical evaluation of Shenqi Fuzheng Injection in relieving anthracycline induced cardiac injury. *Jilin J Tradit Chin Med*. 2012;32:1237-1239.
44. Li XL, Tian QY, Ma WJ. Clinical observation of Shenqi Fuzheng injection combined with chemotherapy in the treatment of advanced breast cancer. *J Mod Oncol*. 2004;(6):574-575.
45. Wu M. Clinical observation of Shenqi Fuzheng Injection in adjuvant treatment of 36 patients with breast cancer after operation. *Gems Health*. 2012;(11):418-419.
46. Song ZJ. Effect-enhancing and toxicity-reducing clinical observation of Shenqi fuzheng injection the treatment of postoperative chemotherapy for breast cancer. *Chin J Clinicians*. 2004;32:62-63.
47. Qiao YC, Cui T. Observation of Shenqi Fuzheng injection combined with Shiroda in the treatment of advanced breast cancer. *Chin J Geriatric Care*. 2013;11:46-47.
48. Kawuli A, Maimaiti A. Effect observation of Shenqi Fuzheng injection combined with chemotherapy in treatment of advanced breast cancer. *Guide China Med*. 2011;9:311-312.
49. Chen JM, Xie X, Liu H, Chen YJ. Clinical observation of Shenqi Fuzheng Injection in patients with advanced breast cancer undergoing chemotherapy. *Mod J Integr Tradit Chin Western Med*. 2010;19:2651-2652.
50. Wang LR, Wang HC, Cao Y. Clinical observation of Shenqi Fuzheng injection in adjuvant treatment of 60 cases of breast cancer. *Chin J Cancer Prevention Treatment*. 2016;23(S2):105-106.
51. Nie JY, Zou TN, Zhang Y, Chen WL. Effect of Shenqi Fuzheng injection combined with chemotherapy on serum CA153 level and immunocyte activity in patients with stage IV breast cancer. *J Practical Oncol*. 2005;(5):452-453.
52. Zhang Q, Cai JB, Chen X, Shi WB, Yang LJ, Zhou J. Shenqi Fuzheng injection combined with chemotherapy for 32 cases of advanced three negative breast cancer. *China Pharmacist*. 2013;16:1866-1867.
53. Li YQ, Peng SP. Shenqi Fuzheng Injection Combined with chemotherapy in the treatment of 35 postoperative breast cancer patients. *Chin J Integr Trad West Med*. 2002;22:827.
54. Shi XG, Ding ZG, Zhang L. Attenuated effect of Shenqi Fuzheng injection on immunosuppression after chemotherapy. *Chin J Exp Tradit Med Formulae*. 2011;17:158-160.
55. Zhang D, Wu J, Liu S, Zhang X, Zhang B. Network meta-analysis of Chinese herbal injections combined with the chemotherapy for the treatment of pancreatic cancer. *Medicine (Baltimore)*. 2017;96:e7005.
56. Dai JF, Zhao Y, Sun YZ. Etiology and pathogenesis of breast cancer. *Guangming Tradit Chin Med*. 2017;32:1069-1072.
57. Du J, Chen BC, Fu XQ, et al. In vitro assays suggest Shenqi Fuzheng injection has the potential to alter melanoma immune microenvironment. *J Ethnopharmacol*. 2016;194:15-19.
58. Tin MM, Cho CH, Chan K, James AE, Ko JK. Astragalus saponins induce growth inhibition and apoptosis in human colon cancer cells and tumor xenograft. *Carcinogenesis*. 2007;28:1347-1355.
59. Zhang XP, Li YD, Luo LL, et al. Astragalus saponins and liposome constitute an efficacious adjuvant formulation for cancer vaccines. *Cancer Biother Radiopharm*. 2018;33:25-31.
60. Wu JL, Xu Q, Xie QJ, et al. Antitumor pharmacological effects of Codonopsis pilosula. *Western J Tradit Chin Med*. 2016;29:18-21.
61. Wang K, Wu J, Duan X, et al. Huangqi injection in the treatment of chronic heart failure: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2017;96:e8167.