Long-acting versus short-acting granulocyte colony-stimulating factors among cancer patients after chemotherapy in China: a systematic review and meta-analysis

Genzhu Wang, PhD\textsuperscript{a}, Yonghe Zhang, MS\textsuperscript{b}, Xiaoying Wang, PhD\textsuperscript{a}, Qiang Sun, MS\textsuperscript{a}, Zhikun Xun, BS\textsuperscript{a}, Minglu Yuan, MS\textsuperscript{a}, Zhongdong Li, MD, PhD\textsuperscript{a}∗\textsuperscript{a}

Abstract

Background: Granulocyte colony-stimulating factors (G-CSFs) include long-acting ones and short-acting ones. They have been mainly applied in Chinese clinical practice for years to prevent neutropenia. However, which type of G-CSF is more superior has not been conclusively determined.

Methods: A systematic literature search was conducted using the PubMed, Embase, Cochrane Library, clinical trials.gov, China National Knowledge Infrastructure, and WAN FANG databases for related studies published till August 2021. Revman 5.3 software was used to assess the effectiveness and safety of these 2 types of G-CSFs in patients undergoing chemotherapy.

Results: Ten studies involving 1916 patients were included in our meta-analysis to compare the effectiveness and safety of long-acting G-CSFs and short-acting G-CSFs. We found that the incidence of febrile neutropenia (relative risk [RR] 0.82; 95% confidence interval [CI] 0.57–1.17), the recovery time of the absolute neutrophil count (mean difference −0.23; 95% CI −0.49 to 0.03), and the fatigue rate (RR 0.82; 95% CI 0.62–1.07) were similar between the long- and the short-acting G-CSFs. However, the long-acting G-CSFs significantly decreased the incidence (RR 0.86; 95% CI 0.76–0.96) and shortened the duration (mean difference −0.19; 95% CI −0.38 to 0.00) of severe (grade ≥3) neutropenia, and decreased the rate of bone and/or muscle pain (RR 0.75; 95% CI 0.58–0.98).

Conclusion: Primary prophylaxis with long-acting G-CSFs was more effective and safer than primary prophylaxis with short-acting G-CSFs in Chinese adults undergoing chemotherapy.

Abbreviations: G-CSFs = granulocyte colony-stimulating factors, ANC = absolute neutrophil count, PEG = polyethylene glycol, RCT = randomized controlled trial, RR = relative risk, CI = confidence interval, MD = mean difference.

Keywords: cancer patients, China, granulocyte colony-stimulating factors, meta-analysis

1. Introduction

Cancer has become a leading cause of death, and in 2018, about 30% of all cancer-related deaths occurred in China.\textsuperscript{[1]} While in 2020, an estimated 4.6 million newly diagnosed cancer cases and 3 million cancer deaths occurred in China.\textsuperscript{[2]} Hence the cancer burden of China was continuously increased, although new therapeutic approaches, including anti-tumor vaccines, immune checkpoint inhibitors, and chimeric antigen receptor T cells, have been shown to be very promising, chemotherapy still plays an important role in cancer treatment.\textsuperscript{[3]} However, chemotherapeutic drugs have a narrow therapeutic window, and are often limited by serious side effects, including febrile neutropenia and severe (grade 3/4) neutropenia.\textsuperscript{[4]} These side effects lead to a delay in chemotherapy, make patients refuse treatment,\textsuperscript{[5]} and are associated with substantial morbidity and mortality.\textsuperscript{[6,7]}

Granulocyte colony-stimulating factors (G-CSFs) can stimulate the proliferation and differentiation of neutrophil precursors, and the production of mature and functional neutrophils.\textsuperscript{[8]} G-CSFs, important supportive care biologics, have been shown to decrease the incidence of febrile neutropenia and reduce the incidence/duration of severe (grade ≥3) neutropenia.\textsuperscript{[9]} The incidence and type of adverse events are diverse (e.g., insomnia, anorexia,
nausea, vomiting, alopecia, fatigue) in the course of G-CSF treatment.\(^9\) Bone/muscle pain is one of the most severe adverse events associated with G-CSF treatment.

Filgrastim, pegfilgrastim, and mencepegfilgrastim are the commonly used G-CSFs in clinical practice in China. Filgrastima is a short-acting G-CSF and is administered an average of 11 doses per chemotherapy cycle for recovery to the normal range of the absolute neutrophil count (ANC).\(^7,10,11\) Pegfilgrastim is produced by the covalent attachment of a 20-kDa polyethylene glycol (PEG) moiety to the N-terminal methionine residue of filgrastim.\(^12\) Mecapegfilgrastim is developed by cross linking 19-kDa PEG and the N-terminal of filgrastim at a fixed-point by covalent amide bond.\(^13\) Pegfilgrastim and mencepegfilgrastim are long-acting G-CSFs and a single dose is administered per chemotherapy cycle, making them more convenient for patients.\(^14,15\) In clinical practice, reducing the number of injections can help improve patients’ treatment compliance.\(^16\)

Several meta-analyses have reported the difference in the efficacy and safety profiles of the G-CSFs.\(^7,17–20\) However, the conclusions were inconsistent and no meta-analysis focused only on Chinese patients. Considering the numerous randomized controlled trials (RCTs) involved in assessing the efficacy and safety of G-CSFs, we performed a systematic review and meta-analysis to evaluate which type of G-CSF was more superior in Chinese cancer patients who received chemotherapy.

2. Materials and methods

We conducted and reported this systematic review according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines.\(^21\) A systematic search was undertaken to identify studies about filgrastim, pegfilgrastim, or mencepegfilgrastim compared with one another for efficacy and safety following chemotherapy in Chinese cancer patients. All data utilized in our meta-analysis were extracted from publicly available material; therefore, ethical approval is waived.

2.1. Protocol and registration

This review has been registered on the PROSPERO website as No. CRD42020163545 (To enable PROSPERO to focus on COVID-19 registrations during the 2020 pandemic, this registration record was automatically published exactly as submitted. The PROSPERO team has not checked eligibility).

2.2. Database and search strategy

We searched the literature on filgrastim, pegfilgrastim, or mencepegfilgrastim using the PubMed, Embase, clinicaltrials.gov, Cochrane Library, WANFANG DATA, and China National Knowledge Infrastructure databases up to August, 2021 without language restrictions. The following keywords were used: G-CSF, filgrastim, pegfilgrastim, mencepegfilgrastim, cancer, and Chinese or China. In addition, the reference lists of the selected manuscripts and reviews were also manually screened.

2.3. Selection of studies and determination of criteria for eligibility

Three reviewers independently screened the titles and abstracts of studies based on predefined inclusion and exclusion criteria and resolved any disagreements through discussion. Next, we retrieved the full texts of each potentially eligible article identified in the screening. Two reviewers independently assessed the articles for inclusion. The reviewers resolved any discrepancies through discussion or, if necessary, by seeking a decision from a third reviewer.

2.3.1. Inclusion criteria. Eligible studies were required to satisfy the following criteria: (1) study population: adult cancer patients; (2) versus different G-CSFs; (3) study design: comparative studies and only RCTs were included; and (4) outcome: clinical efficacy and/or safety outcomes.

2.3.2. Exclusion criteria. We excluded (1) no comparative studies evaluating the clinical efficacy and/or safety of G-CSFs in oncology (e.g., reviews, expert comments, and clinical guidelines); (2) studies without comparators; (3) studies with insufficient data to calculate effect sizes (e.g., the clinical effects were shown by onset time and the side effect were shown by remission time, and the clinical effects were calculated using cycles of chemotherapy); (4) crossover studies; (5) duplicate studies. If the same study was reported in more than one publication, we only included the most informative article to avoid duplication of information; (6) studies using G-CSFs for stem cell mobilization in bone marrow or peripheral blood stem cell transplantation.

2.4. Quality assessment

The Cochrane Collaboration’s tool was used to assess the risk of bias.\(^22\) The reviewers resolved any discrepancy through discussion or, if necessary, by seeking a decision from a third reviewer.

2.5. Outcome Measures

2.5.1. Efficacy outcomes.

1. Incidence of febrile neutropenia: the proportion of patients with an ANC < 0.5 × 10^9/L and temperature ≥ 38.2°C.\(^23\) Febrile neutropenia was the main and severe adverse event for many chemotherapy regimens and it was always chosen as a key clinical outcome due to its direct bearing on morbidity, mortality and hospitalization rates.\(^17\)

2. Incidence of severe (grade ≥3) neutropenia: the proportion of patients with ANC < 1 × 10^9/L.\(^7\)

3. Duration of severe (grade ≥3) neutropenia: the number of consecutive days in which a patient had ANC < 1 × 10^9/L.\(^18\)

4. Time to ANC recovery: days from ANC nadir (lowest ANC), counted as the total number of days of ANC ≥ 2.0 × 10^9/L.\(^24\)

2.5.2. Safety outcomes.

1. Bone/muscle pain rate: the most severe adverse event associated with G-CSF treatment.\(^9\)

2. Fatigue rate: one of the common adverse clinical events in the course of G-CSF drug treatment.

2.6. Data extraction

The following information was obtained from each eligible study: basic information (first author, age, year of publication, and location), chemotherapy regimen, tumor type, primary or secondary prophylaxis. Two reviewers independently extracted data from the selected studies using a form developed for this
review. The reviewers resolved any discrepancy through discussion or, if necessary, by seeking a decision from a third reviewer.

2.7. Data synthesis

Meta-analyses were undertaken to compare the efficacy and/or safety outcomes of long-acting and short-acting G-CSFs. Analyses were undertaken using RevMan software (version 5.3). For binary outcomes, results were presented as a pooled relative risk (RR) and 95% confidence intervals (CIs); for continuous outcomes, results were expressed as mean differences (MDs) with 95% CIs. Statistical significance was defined as \( p < 0.05 \). Heterogeneity was presented using the \( I^2 \) statistic, which describes the percentage of the variability in effective estimates that is due to heterogeneity rather than sampling error. When \( I^2 > 50\% \), heterogeneity was considered significant and a random-effect model was used. Otherwise, a fixed-effect model was used.\(^{[18]}\) The 100 \( \mu \)g/kg and/or fixed 6mg dose regimen commonly was used in the primary prophylaxis due to its efficacy and safety profiles.\(^{[25,26]}\) A higher rate of neutropenia induced by chemotherapy often occurred in breast cancer due to dose-dense chemotherapy regimens.\(^{[27]}\) Subgroup analyses were performed according to the doses of long-acting G-CSFs and cancer type.

3. Results

The full-text screening process is presented in a preferred reporting items for systematic reviews and meta-analysis (PRISMA) diagram according to the inclusion and exclusion procedures (Fig. 1). The databases and manual searches yielded 976 potentially relevant records. After titles, abstracts, and full texts were screened, 10 studies of short-acting G-CSFs versus long-acting G-CSFs were ultimately included in the meta-analysis (Fig. 1).

3.1. Characteristics of the included studies

Characteristics of the included studies are described in Table 1. The 10 studies were published from 2014 to 2020. The long-acting G-CSFs versus short-acting G-CSFs studies were conducted in populations with early-stage breast cancer, cervical cancer, and colorectal cancer patients. The random sequence generation and allocation concealment methods were not given in most of the studies. Details of the risk of bias assessment are presented in Figure 2.

3.2. Synthesis of results

Ten studies containing 1916 patients were included in the analysis of long-acting G-CSFs versus short acting G-CSFs. As

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**Figure 1.** PRISMA flowchart of the literature search.
| Author          | Year | Study design | Location | Patients no. | Age      | Tumor type         | Chemotherapy regimen | Primary or secondary prophylaxis | G-CSF type | G-CSF dose | G-CSF type | G-CSF dose |
|-----------------|------|--------------|----------|--------------|----------|-------------------|----------------------|---------------------------|-------------|------------|-------------|------------|
| Dong et al[38]  | 2014 | RCT         | Jiangxi  | 60           | 32–58    | Breast cancer TAC | Pegfilgrastim         | Primary                   | Pegfilgrastim | 3 mg       | Pegfilgrastim | 150 µg/d   |
| Zhang et al[26] | 2015 | RCT         | Shaanxi  | 171          | 18–65    | Breast cancer TAC | Pegfilgrastim         | Primary                   | Pegfilgrastim | 100 µg/kg  | Pegfilgrastim | 100 µg/kg  |
| Xu et al[31]    | 2016 | RCT         | Beijing  | 171          | 18–65    | Breast cancer TAC | Pegfilgrastim         | Primary                   | Pegfilgrastim | 60 µg/kg   | Pegfilgrastim | 120 µg/kg  |
| Xu et al[36]    | 2017 | RCT         | Beijing  | 569          | 39–58    | Breast cancer EC, ET, TC | Pegfilgrastim         | Primary                   | Pegfilgrastim | 100 µg/kg  | Pegfilgrastim | 100 µg/kg  |
| Chi et al[58]   | 2018 | RCT         | Shanghai | 68           | 50–71    | Colorectal cancer FOLFOX 4 | Pegfilgrastim         | Primary                   | Pegfilgrastim | ≥45 kg Fixed 6 mg; <45 kg Fixed 3 mg | Pegfilgrastim | 300 µg/kg; <45 kg Fixed 150 µg |
| Jiang et al[42] | 2018 | RCT         | Beijing  | 215          | 18–70    | Breast cancer AC, EC, AT, TC, etc. | Pegfilgrastim         | Primary                   | Pegfilgrastim | 60 µg/kg   | Pegfilgrastim | 5 µg/kg    |
| Wu et al[40]    | 2018 | RCT         | Jiangsu  | 89           | 20–68    | Breast cancer ECT | Pegfilgrastim         | Primary                   | Pegfilgrastim | 300 µg/kg  | Pegfilgrastim | 5 µg/kg    |
| Xu et al[52]    | 2019 | RCT         | Beijing  | 331          | 18–70    | Breast cancer AC, AT | Pegfilgrastim         | Primary                   | Pegfilgrastim | 300 µg/kg  | Pegfilgrastim | 5 µg/kg    |
| Wang et al[41]  | 2019 | RCT         | Beijing  | 182          | 18–70    | Breast cancer AC, AT | Pegfilgrastim         | Primary                   | Pegfilgrastim | 100 µg/kg  | Pegfilgrastim | 100 µg/kg  |
| Ma et al[43]    | 2020 | RCT         | Henan    | 60           | 26–83    | Cervical cancer Chemoradiotherapy | Pegfilgrastim         | Primary                   | Pegfilgrastim | 60 µg/kg   | Pegfilgrastim | 150 µg/d   |

AC=adriamycin + cyclophosphamide, AT=adriamycin + docetaxel, EC=epirubicin + cyclophosphamide, ECT=epirubicin + cyclophosphamide + docetaxel, ET=epirubicin + docetaxel, FOLFOX 4=oxaliplatin + leucovorin + 5-fluorouracil, G-CSFs=granulocyte colony-stimulating factors, RCT=randomized controlled trial, rhG-CSF=recombinant human granulocyte colony stimulating factor, TAC=docetaxel + adriamycin + cyclophosphamide, TC=docetaxel + cyclophosphamide.
shown in Figure 3, meta-analysis suggested no significant difference in terms of incidence of febrile neutropenia (RR 0.82; 95% CI 0.57–1.17; $I^2=0\%$) between long- and short-acting G-CSFs. Similar results were also found in our subgroup analyses, see Table 2.

For the incidence/duration of severe (grade ≥3) neutropenia, the long-acting G-CSFs significantly decreased the incidence (RR 0.86; 95% CI 0.76–0.96; $I^2=62\%$) and shortened the duration (MD $–0.19; 95\%$ CI $–0.38$ to $0.00; I^2=71\%$) of severe (grade ≥3) neutropenia compared with short-acting G-CSFs. Our subgroup analyses also displayed the same phenomenon (Table 2). Although high heterogeneities existed in all these meta-analyses, our sensitivity analysis showed similar findings by the sequential omission of each study.

The pooled analysis of time to ANC recovery showed there was no significant difference (MD $–0.23; 95\%$ CI $–0.49$ to $0.03; I^2=49\%$) between long- and short-acting G-CSFs. However, subgroup analysis on the patients with limited doses (100 μg/kg or fixed 6 mg) of long-acting G-CSFs displayed that long-acting G-CSFs had a shorter recovery time than short-acting G-CSFs (MD $–0.49; 95\%$ CI $–0.88$ to $–0.10; I^2=57\%$).

Eight studies reported the safety profiles of long- and short-acting G-CSFs. As shown in Figure 4, long-acting G-CSFs significantly lowered the incidence of bone/muscle pain (RR 0.75; 95% CI 0.58–0.98; $I^2=39\%$) compared to short-acting G-CSFs. Similar results were observed in breast cancer patients and in patients who received treatment regimen containing docetaxel (RR 0.69; 95% CI 0.48–0.98; $I^2=46\%$). Although no significant difference was found in the patients with limited doses of long-acting G-CSFs, there was a trend towards a lower incidence of bone/muscle pain (RR 0.79; 95% CI 0.60–1.05; $I^2=46\%$). Our total and subgroup analyses suggested that there was no significant difference between long- and short-acting G-CSFs in terms of the occurrence of fatigue (Fig. 4 and Table 2).

We did not evaluate the presence of publication bias due to there being <10 studies for any comparison.

4. Discussion
In the present meta-analysis, the effectiveness and safety of long-acting versus short-acting G-CSFs in the prophylaxis of febrile neutropenia induced by chemotherapy were evaluated in Chinese cancer patients. The effectiveness indicators included the incidence of febrile neutropenia, the incidence/duration of severe (grade ≥3) neutropenia, and time to ANC recovery; the occurrences of bone/muscle pain and fatigue were used as safety parameters. We found that long-acting G-CSFs were safer and more effective than short-acting G-CSFs in decreasing the incidence of severe (grade ≥3) neutropenia, the duration of severe (grade ≥3) neutropenia and the occurrence of bone and/or muscle pain. In addition, long-acting G-CSFs was also a cost-effective alternative to short-acting ones. Hence, we recommend that Chinese clinicians should give priority to using long-acting G-CSFs because long-acting G-CSFs are more effective and safer.

The incidence of febrile neutropenia was chosen as a crucial indicator to evaluate the efficacy of the G-CSF drugs. However, conclusions of previous meta-analyses on whether...
Figure 3. Forest plot comparing the effectiveness between long-acting G-CSFs and short-acting G-CSFs. (A) Incidence of febrile neutropenia; (B) Incidence of grade ≥3 neutropenia; (C) Duration of grade ≥3 neutropenia; (D) The time to ANC recovery. ANC = absolute neutrophil count, G-CSFs = granulocyte colony-stimulating factors.
long-acting G-CSFs were more effective in reducing the occurrence of febrile neutropenia were not consistent.\cite{17,30} Cooper et al\cite{7} only included Australia and USA patients in their meta-analysis and concluded long-acting G-CSFs were more effective than short-acting G-CSFs in reducing the incidence of febrile neutropenia. Wang et al\cite{17} also demonstrated long-acting G-CSFs were superior to short-acting G-CSFs in their meta-analysis, which included crossover studies. However, Li et al\cite{30} showed long-acting G-CSFs had no obvious advantage over short-acting G-CSFs in the breast cancer patient population. We excluded crossover studies from our meta-analysis, and found no significant difference in reducing the incidence of febrile neutropenia between long- and short-acting G-CSFs in Chinese cancer patients. Similar results were also demonstrated in our subgroup analyses, including the breast cancer patient population and the patient population with limited doses of long-acting G-CSFs.

The reduced incidence and duration of severe (grade ≥3) neutropenia were also important indicators of the efficacy of G-CSFs.\cite{16} Our results showed long-acting G-CSFs were more effective than short-acting G-CSFs in reducing the incidence and duration of severe neutropenia. These results were inconsistent with those by Li et al,\cite{30} who only included breast cancer patients in their meta-analysis, which showed long-acting G-CSFs had no obvious advantage over short-acting G-CSFs. However, our subgroup analysis including only breast cancer patients also showed long-acting G-CSFs were more effective than short-acting G-CSFs. The reason may be we only included Chinese breast cancer patients and excluded crossover studies. Although there were high heterogeneities in our analyses, sensitivity analysis showed that no single study greatly influenced the outcomes. In addition, our further analysis showed the high heterogeneity was caused by Xu et al,\cite{31} whose pegfilgrastim dose regimen was 120 μg/kg (higher dose than the other studies). Time to ANC recovery was another efficacy outcome.\cite{18} Our total analysis showed that there was no significant difference between the 2 groups. But subgroup analysis on limited doses (100 μg/kg or fixed 6 mg) of long-acting G-CSFs displayed that long-acting G-CSFs were superior to short-acting G-CSFs. It was because a 60 μg/kg cycle (lower dose than the one recommended in clinical trials) of a long-acting G-CSF was included in 1 study.\cite{26,32}

All these results indicate that long-acting G-CSFs can provide some clinical benefits. We speculate that its mechanism may be related to a significant decrease the clearance rate of PEGylation filgrastim and prolong the stimulation time on bone marrow.\cite{33,34} However the specific mechanism for such findings remains to be further explored.\cite{25}

Numerous adverse events were reported in the clinical trials.\cite{13,34-36} Bone and/or muscle pain was the most common adverse event related to G-CSF drug treatment.\cite{37} Our total meta-analysis demonstrated long-acting G-CSFs significantly decrease the incidence of bone and/or muscle pain, and similar results were also observed in breast cancer patients and in patients who receiving docetaxel treatment. These results were inconsistent with previous studies, which included foreign cancer patients or which only used a fixed dosage of long-acting G-CSFs.\cite{18,30} Although the limited dose (100 μg/kg or fixed 6 mg) group displayed no significant difference, the long-acting G-CSFs showed a decreasing trend. Fatigue was often reported in the course of G-CSFs treatment.\cite{25,36,38-41} Our total meta-analyses showed no significant difference between the long- and short-acting groups.

### Table 2

| Efficacy and safety profiles | Subgroups | Studies | Long/short-acting G-CSFs | Model | RR/MD | 95% CI | \(P\)% |
|-------------------------------|---------------------------------|---------|--------------------------|-------|-------|-------|-------|
| Incidence of febrile neutropenia | Breast cancer patients | 6       | 1082/556 Fixed           | 0.84  | 0.57–1.23 | 0.0   |
|                               | Patients with limited doses (100 μg/kg or fixed 6 mg) of long-acting G-CSFs | 7       | 948/556 Fixed           | 0.82  | 0.53–1.27 | 0.0   |
| Incidence of severe (grade ≥3) neutropenia | Breast cancer patients | 8       | 1157/600 Random         | 0.86  | 0.76–0.97 | 63    |
|                               | Patients with limited doses (100 μg/kg or fixed 6 mg) of long-acting G-CSFs | 8       | 993/632 Random         | 0.78  | 0.67–0.90 | 57    |
| Duration of severe (grade ≥3) neutropenia | Breast cancer patients | 7       | 1127/600 Random         | −0.19 | −0.39–0.00 | 73    |
|                               | Patients with limited doses (100 μg/kg or fixed 6 mg) of long-acting G-CSFs | 8       | 993/632 Random         | −0.34 | −0.53 to −0.15 | 61    |
| Time to ANC recovery | Breast cancer patients | 4       | 410/236 Fixed           | −0.23 | −0.49 to 0.03 | 49    |
|                               | Patients with limited doses (100 μg/kg or fixed 6 mg) of long-acting G-CSFs | 4       | 240/236 Fixed           | −0.49 | −0.88 to −0.10 | 57    |
| Bone/muscle pain | Breast cancer patients | 6       | 920/481 Fixed           | 0.69  | 0.48–0.98 | 46    |
|                               | Patients with limited doses (100 μg/kg or fixed 6 mg) of long-acting G-CSFs | 7       | 871/513 Fixed           | 0.79  | 0.60–1.05 | 46    |
| Fatigue | Breast cancer patients | 5       | 792/438 Fixed           | 0.81  | 0.61–1.06 | 48    |
|                               | Patients with limited doses (100 μg/kg or fixed 6 mg) of long-acting G-CSFs | 5       | 792/440 Fixed           | 0.81  | 0.61–1.07 | 49    |

ANC = absolute neutrophil count, CI = confidence interval, G-CSFs = granulocyte colony-stimulating factors, MD = mean difference, RR = relative risk.
4.1. Strengths and limitations

To the best of our knowledge, this is the first meta-analysis to assess the efficacy and safety of different G-CSFs in the Chinese patient population. Despite these strengths, including that only RCTs were included and sensitivity analysis showed that no single study greatly influenced the outcomes, some limitations to our systematic review exist. First, there was heterogeneity among trials, which may be related to cancer type, races, the dose of G-CSF, patients' disease stages, chemotherapy regimen, numbers of chemotherapy cycles and cycle length. Second, most studies were open-label rather than double-blind. Third, we could not analyze publication bias using funnel plots, as there were <10 studies for each outcome. Forth, our studies included for analysis were mainly involved in breast cancer patients. Whether it is suitable for other cancer patients remains to be further studied. In addition, although different databases were searched to find related studies, it was still impossible to include all the studies.

5. Conclusion

This systematic review and meta-analysis demonstrate that long-acting G-CSFs are safer and more effective than short-acting G-CSFs for early-stage Chinese cancer patients. Considering that the long-acting G-CSFs are more convenient and cost-effective in clinical practice, our findings will further strengthen the clinician’s confidence in using long-acting G-CSFs prophylaxis in patients undergoing chemotherapy, especially in corona virus disease 2019 period.

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Author contributions

All of the authors have read and approved the final manuscript. GZW, YHZ, and ZDL conceived and designed the study. XYW,
QS, MLY, ZKK, and YHZ took full responsibility for data collecting. XYW, YHZ, and GZW performed the meta-analysis, systematic review, and drafted the manuscript. YHZ and ZDL helped revise the manuscript.

Conceptualization: Zhong-dong Li.
Data curation: Zhi-kun Xin, Ming-lu Yuan.
Investigation: Geng-zhu Wang.
Methodology: Yong-he Zhang, Xiao-ying Wang.
Project administration: Zhong-dong Li.
Resources: Xiao-ying Wang, Qiang Sun, Zhi-kun Xin.
Software: Qiang Sun.
Validation: Xiao-ying Wang.
Writing – original draft: Geng-zhu Wang.
Writing – review & editing: Yong-he Zhang, Zhong-dong Li.

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