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Long-acting versus short-acting granulocyte colony-stimulating factors among cancer patients after chemotherapy in China
A systematic review and meta-analysis of randomized controlled trials

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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.[1] While in 2020, an estimated 4.6 million newly diagnosed cancer cases and 3 million cancer deaths occurred in China.[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.[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.[4] These side effects lead to a delay in chemotherapy, make patients refuse treatment,[5] and are associated with substantial morbidity and mortality.[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.[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.[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 mecapegfilgrastim 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 mecapegfilgrastim 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 mecapegfilgrastim 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 mecapegfilgrastim 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, mecapegfilgrastim, 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 $ANC < 0.5 \times 10^9/L$ and temperature $\geq 38.2°C$.[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 $ANC < 1 \times 10^9/L$.[7]
3. Duration of severe (grade ≥3) neutropenia: the number of consecutive days in which a patient had $ANC < 1 \times 10^9/L$.[18]
4. Time to ANC recovery: days from ANC nadir (lowest ANC), counted as the total number of days of $ANC \geq 2.0 \times 10^9/L$.[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 μg/kg and/or fixed 6 mg 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
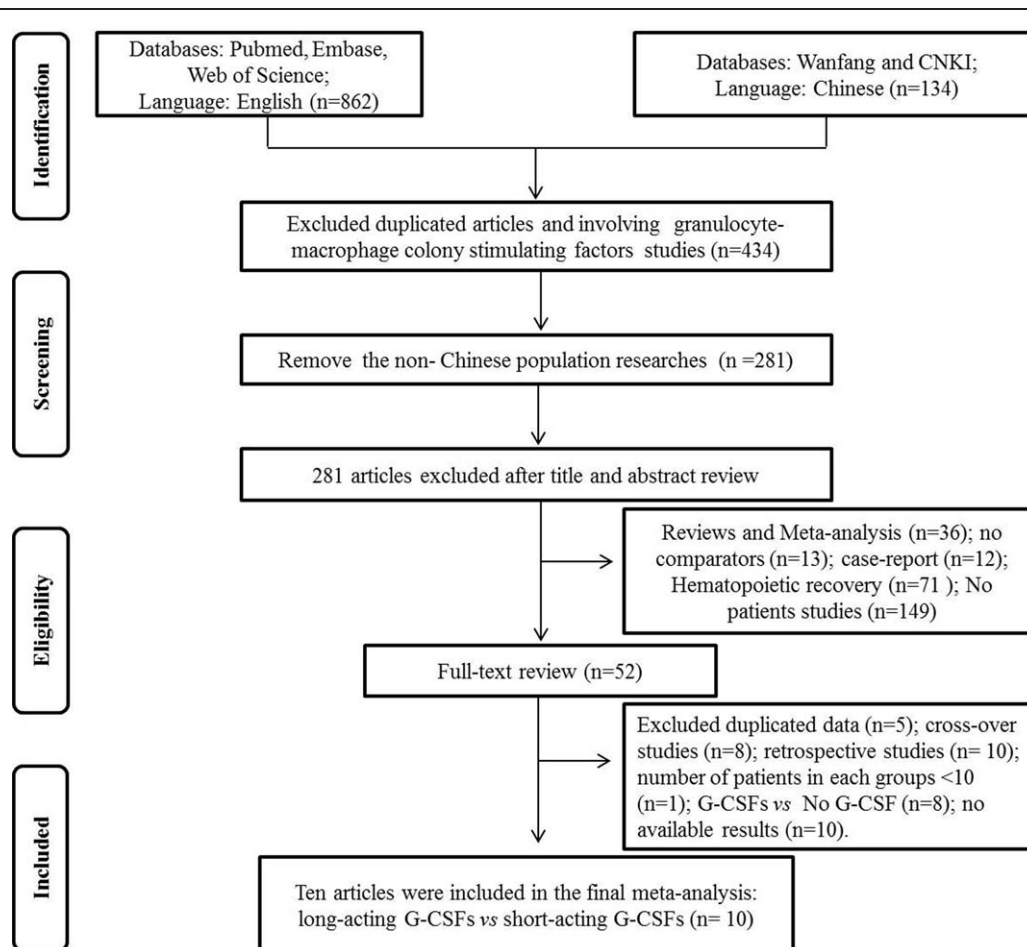

Figure 1. PRISMA flowchart of the literature search.

Table 1

Characteristics of included studies.

Author	Year	Study design	Location	Patients no.	Age	Tumor type	Chemotherapy regimen	Primary or secondary prophylaxis	Long-acting G-CSFs group		Short-acting G-CSFs group	
									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	Primary	Pegfilgrastim	Fixed 3 mg	rhG-CSF	150 µg/d
Zhang et al[26]	2015	RCT	Shaanxi	171	18–65	Breast cancer	TAC	Primary	Pegfilgrastim	60 µg/kg 100 µg/kg 120 µg/kg	filgrastim	5 µg/kg
Xu et al[31]	2016	RCT	Beijing	171	18–65	Breast cancer	TAC	Primary	Pegfilgrastim	60 µg/kg 100 µg/kg 120 µg/kg	rhG-CSF	5 µg/kg
Xie et al[36]	2017	RCT	Shanghai	569	39–58	Breast cancer	EC, ET, TC	Primary	Pegfilgrastim	100 µg/kg Fixed 6 mg	rhG-CSF	5 µg/kg
Chi et al[39]	2018	RCT	Shanxi	68	50–71	Colorectal cancer	FOLFOX 4	Primary	Pegfilgrastim	100 µg/kg	rhG-CSF	5 µg/kg
Jiang et al[42]	2018	RCT	Beijing	215	18–70	Breast cancer	AC, EC, AT, TC, etc.	Primary	Pegfilgrastim	≥45 kg Fixed 6 mg; <45 kg Fixed 3 mg	rhG-CSF	≥45kg Fixed 300 µg; <45kg Fixed 150 µg
Wu et al[40]	2018	RCT	Jiangsu	89	20–68	Breast cancer	ECT	Primary	Pegfilgrastim	100 µg/kg	rhG-CSF	5 µg/kg
Xu et al[25]	2019	RCT	Beijing	331	18–70	Breast cancer	AC, AT	Primary	Meca-pegfilgrastim	100 µg/kg Fixed 6 mg	rhG-CSF	5 µg/kg
Wang et al[41]	2019	RCT	Beijing	182	18–70	Breast cancer	AC, AT	Primary	Meca-pegfilgrastim	100 µg/kg	G-CSF	5 µg/kg
Ma et al[43]	2020	RCT	Henan	60	26–83	Cervical cancer	Chemoradiotherapy	Primary	pegfilgrastim	Fixed 6 mg	rhG-CSF	150 µg/d

AC = adriamycin + cyclophosphamide, AT = adriamycin + docetaxel, EC = epirubicin + cyclophosphamide, ECT = epirubicin + cyclophosphamide + docetaxel, ET = epirubicin + docetaxel, FOLFOX 4 = oxaliplatin + levoleucovorin + 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.
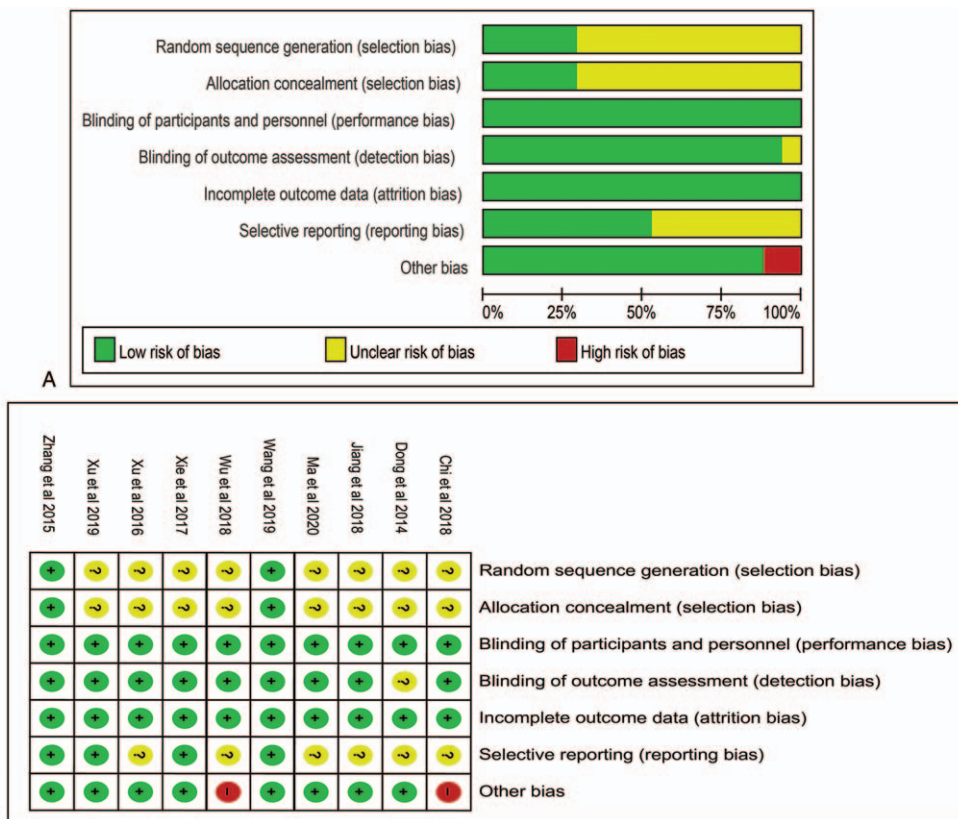
Figure 2. Risk of bias for included studies. (A) Summary of risk of bias; (B) Each risk of bias item for each included study.

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.[28]

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.[29] 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.[17] However, conclusions of previous meta-analyses on whether
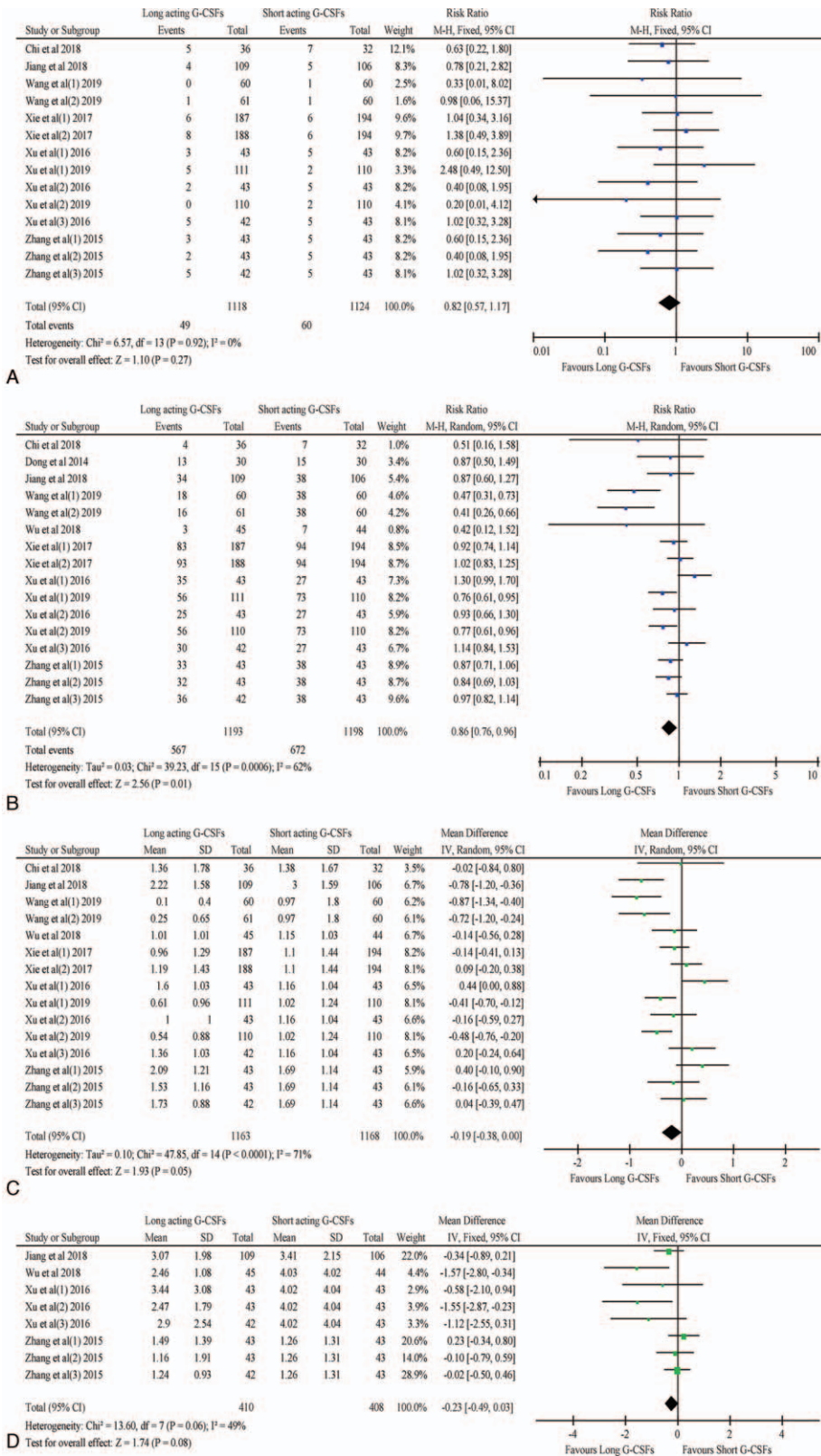
Figure 3. Forest plot comparing the effectiveness between long-acting G-CSFs and short-acting G-CSFs. (A) Incidence of febrile neutropenia; (B) Incidence of grade ≥3 neutropenia; (C) Duration of grade ≥3 neutropenia; (D) The time to ANC recovery. ANC = absolute neutrophil count, G-CSFs = granulocyte colony-stimulating factors.

Table 2

Sub-group analysis the efficacy and toxicity of long- and short-acting G-CSFs.

Efficacy and safety profiles	Subgroups	Studies	Long/short-acting G-CSFs	Model	RR/MD	95% CI	I^2%
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 00 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	798/440	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.

long-acting G-CSFs were more effective in reducing the occurrence of febrile neutropenia were not consistent.[7,17,30] Cooper et al[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[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[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.[30] 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,[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,[31] whose pegfilgrastim dose regimen was 120 µg/kg (higher dose than the other studies). Time to ANC recovery was another efficacy outcome.[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.[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.[33,34] However the specific mechanism for such findings remains to be further explored.[25]

Numerous adverse events were reported in the clinical trials.[13,34–36] Bone and/or muscle pain was the most common adverse event related to G-CSF drug treatment.[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.[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.[25,36,38–41] Our total meta-analyses showed no significant difference between the long- and short-acting groups.
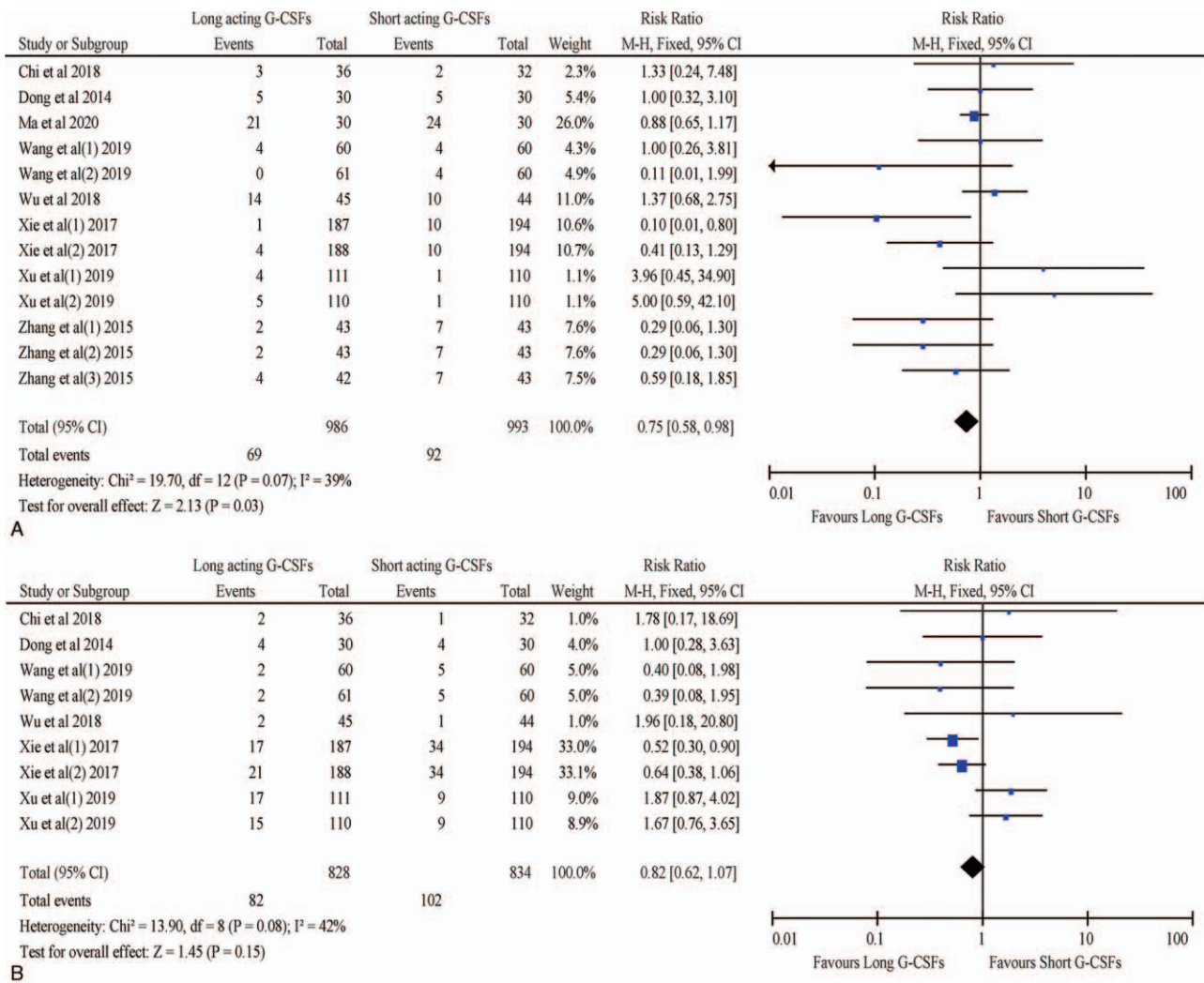
Study or Subgroup	Long acting G-CSFs Events	Total	Short acting G-CSFs Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Chi et al 2018	3	36	2	32	2.3%	1.33 [0.24, 7.48]	
Dong et al 2014	5	30	5	30	5.4%	1.00 [0.32, 3.10]	
Ma et al 2020	21	30	24	30	26.0%	0.88 [0.65, 1.17]	
Wang et al(1) 2019	4	60	4	60	4.3%	1.00 [0.26, 3.81]	
Wang et al(2) 2019	0	61	4	60	4.9%	0.11 [0.01, 1.99]	
Wu et al 2018	14	45	10	44	11.0%	1.37 [0.68, 2.75]	
Xie et al(1) 2017	1	187	10	194	10.6%	0.10 [0.01, 0.80]	
Xie et al(2) 2017	4	188	10	194	10.7%	0.41 [0.13, 1.29]	
Xu et al(1) 2019	4	111	1	110	1.1%	3.96 [0.45, 34.90]	
Xu et al(2) 2019	5	110	1	110	1.1%	5.00 [0.59, 42.10]	
Zhang et al(1) 2015	2	43	7	43	7.6%	0.29 [0.06, 1.30]	
Zhang et al(2) 2015	2	43	7	43	7.6%	0.29 [0.06, 1.30]	
Zhang et al(3) 2015	4	42	7	43	7.5%	0.59 [0.18, 1.85]	
Total (95% CI)		**986**		**993**	**100.0%**	**0.75 [0.58, 0.98]**	
Total events	69		92				

Heterogeneity: Chi² = 19.70, df = 12 (P = 0.07); I² = 39%
Test for overall effect: Z = 2.13 (P = 0.03)

A

Study or Subgroup	Long acting G-CSFs Events	Total	Short acting G-CSFs Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Chi et al 2018	2	36	1	32	1.0%	1.78 [0.17, 18.69]	
Dong et al 2014	4	30	4	30	4.0%	1.00 [0.28, 3.63]	
Wang et al(1) 2019	2	60	5	60	5.0%	0.40 [0.08, 1.98]	
Wang et al(2) 2019	2	61	5	60	5.0%	0.39 [0.08, 1.95]	
Wu et al 2018	2	45	1	44	1.0%	1.96 [0.18, 20.80]	
Xie et al(1) 2017	17	187	34	194	33.0%	0.52 [0.30, 0.90]	
Xie et al(2) 2017	21	188	34	194	33.1%	0.64 [0.38, 1.06]	
Xu et al(1) 2019	17	111	9	110	9.0%	1.87 [0.87, 4.02]	
Xu et al(2) 2019	15	110	9	110	8.9%	1.67 [0.76, 3.65]	
Total (95% CI)		**828**		**834**	**100.0%**	**0.82 [0.62, 1.07]**	
Total events	82		102				

Heterogeneity: Chi² = 13.90, df = 8 (P = 0.08); I² = 42%
Test for overall effect: Z = 1.45 (P = 0.15)

B

Figure 4. Forest plot comparing the results of safety between long-acting G-CSFs and short-acting G-CSFs. (A) Incidence of bone and/or muscle pain; (B) Incidence of fatigue. G-CSFs = granulocyte colony-stimulating factors.

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.

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, ZKX, 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.

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Software: Qiang Sun.
Validation: Xiaoying Wang.
Writing – original draft: Genzhu Wang.
Writing – review & editing: Yonghe Zhang, Zhong-dong Li.

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