



Safety and Efficacy of Filgrastim in the Prevention of Chemotherapy-Induced Neutropenia: A PRISMA 2020-Compliant Systematic Review and Meta-Analysis

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Article Information	ABSTRACT
<i>Systematic Review and Meta-Analysis</i>	Background: Chemotherapy-induced neutropenia (CIN) and febrile neutropenia (FN) represent the most prevalent and clinically consequential dose-limiting toxicities of myelosuppressive cancer therapy. Filgrastim (recombinant human granulocyte colony-stimulating factor; rhG-CSF) has been used as primary and secondary prophylaxis of CIN for more than three decades, yet pooled effect estimates and heterogeneity quantification from the full body of randomized evidence have not been formally synthesized under PRISMA 2020 standards. Objectives: To systematically review and meta-analyse randomized controlled trials (RCTs) evaluating filgrastim versus placebo or no treatment for the prevention of CIN in adult cancer patients receiving cytotoxic chemotherapy, with primary focus on FN incidence and pre-specified secondary outcomes. Eligibility Criteria: RCTs in adult patients with non-myeloid malignancies receiving filgrastim 5 mcg/kg/day SC/IV versus placebo or no treatment, reporting FN or grade 3/4 neutropenia outcomes. Non-English publications and paediatric trials (<18 years) were excluded. Information Sources: PubMed/MEDLINE (1991–2025), EMBASE, Cochrane CENTRAL, ClinicalTrials.gov, WHO ICTRP, and reference lists of eligible studies and prior systematic reviews. Risk of Bias: Assessed using the Cochrane Risk of Bias tool version 2 (RoB 2) for RCTs. Certainty of evidence evaluated using GRADE methodology. Synthesis: Random-effects meta-analysis using the Der Simonian-Laird method. Summary relative risk (RR) with 95% confidence intervals (CI), Cochran Q-test for heterogeneity, I ² statistic, tau ² for between-study variance. Funnel plot asymmetry assessed by Egger's test. Results: Eleven RCTs (n=2,553 patients) met eligibility for the primary analysis. Filgrastim significantly reduced FN incidence versus placebo/no treatment (pooled RR 0.58; 95% CI 0.50–0.67; I ² =35.4%; Q=17.0; p=0.11), corresponding to a 42% relative risk reduction and a number needed to treat (NNT) of 5.3. Grade 3/4 neutropenia was also significantly reduced (RR 0.50; 95% CI 0.37–0.68; I ² =48.2%). Duration of severe neutropenia was shortened by a mean of 3.8 days (95% CI 2.9–4.7). Bone pain occurred more frequently with filgrastim (RR 2.61; 95% CI 1.29–5.27). No statistically significant increase in
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serious adverse events was observed. Certainty of evidence: HIGH for FN incidence; MODERATE for grade 3/4 neutropenia and bone pain. No significant publication bias detected (Egger $p=0.18$). Conclusions: This PRISMA 2020-compliant meta-analysis provides high-certainty evidence that filgrastim substantially and significantly reduces FN incidence in adult cancer patients receiving myelosuppressive chemotherapy. The safety profile is acceptable. These findings support guideline-concordant use and the equivalence of biosimilar formulations. Registration: PROSPERO CRD420250643093.

1. INTRODUCTION

1.1 Background

Chemotherapy-induced neutropenia (CIN) is the most clinically significant and frequently dose-limiting toxicity of myelosuppressive anticancer regimens. CIN arises from the direct cytotoxic effects of chemotherapeutic agents on rapidly proliferating bone marrow myeloid progenitors, resulting in a predictable nadir in circulating neutrophils 7-14 days following drug administration.^[1,2] The most serious consequence of CIN is febrile neutropenia (FN), characterized by an absolute neutrophil count (ANC) $<0.5 \times 10^9/L$ in association with a temperature $\geq 38.3^\circ C$ or sustained temperature $\geq 38.0^\circ C$ for >1 hour. FN is a medical emergency associated with an in-hospital mortality rate of 2.6-7.0% in patients with solid tumors, rising to 7.4% in those with hematologic malignancies.^[3,4] Each episode of FN necessitates inpatient hospitalization in approximately 83% of cases, generating average treatment costs exceeding \$40,000 per episode in the United States and €12,000-€35,000 in European healthcare systems.^[4,5] Filgrastim (recombinant methionyl human G-CSF; r-met HUG-CSF; Neupogen®, Amgen Inc.) was the first recombinant growth factor approved by the U.S. FDA (1991) for the prevention and treatment of CIN. It acts by binding to the granulocyte colony-stimulating factor receptor (G-CSFR), activating the JAK2/STAT3 signaling cascade, thereby stimulating proliferation, differentiation, and functional activation of neutrophil progenitors.^[6,7] While multiple meta-analyses have addressed aspects of filgrastim's efficacy,^[8,9,10] none has applied the comprehensive PRISMA 2020 reporting framework, which introduced updated guidance on search documentation, risk of bias assessment, certainty of evidence grading, and selective reporting evaluation. This systematic review and meta-analysis were undertaken to address this gap and to provide a definitive, transparently reported synthesis of the randomized controlled evidence base.

1.2 Rationale for Update

An updated meta-analysis is warranted for the following reasons: (1) significant new RCT data have emerged since the most recent comprehensive meta-analysis (2021); (2) PRISMA 2020 requirements mandate additional methodological transparency not present in prior syntheses; (3) the GRADE framework has not been formally applied to the filgrastim CIN evidence base; (4) biosimilar data necessitate updated comparative syntheses; and (5) subgroup analyses by cancer type, chemotherapy regimen intensity, and patient age have not been systematically conducted.

3 Objectives

This systematic review and meta-analysis address the following pre-specified PICO-structured research questions:

PICO Element	Specification
Population (P)	Adult patients (≥ 18 years) with non-myeloid malignancies (solid tumors, non-Hodgkin lymphoma, Hodgkin lymphoma) receiving cytotoxic myelosuppressive chemotherapy
Intervention (I)	Filgrastim (r-met HUG-CSF) 5 mcg/kg/day SC or IV, initiated 24-72 hours after chemotherapy, for primary prophylaxis of CIN
Comparator (C)	Placebo injection or no treatment (observation only)

Outcome 1 – Primary	Incidence of febrile neutropenia (FN): ANC $<0.5 \times 10^9/L$ + fever (temperature ≥ 38.2 - $38.3^\circ C$); measured per patient or per cycle as reported
Outcome 2	Incidence of grade 3/4 neutropenia per NCI-CTCAE
Outcome 3	Duration of severe neutropenia (days with ANC $<0.5 \times 10^9/L$)
Outcome 4	Infection-related hospitalizations and antibiotic use
Outcome 5	Overall survival (OS) and infection-related mortality
Outcome 6	Safety: incidence of bone pain, splenomegaly, and serious adverse events (SAEs)
Study Design	Randomized controlled trials (RCTs) only

2. METHODS

This systematic review and meta-analysis were prospectively registered with PROSPERO (registration: CRD420250643093) and conducted in full accordance with the PRISMA 2020 statement (Page et al., 2021). A pre-specified protocol was developed and adhered to throughout all phases of the review.

2.1 Eligibility Criteria

2.1.1 Inclusion Criteria

- *Study design*: Randomized controlled trials (RCTs), parallel-group or crossover design
- *Population*: Adult patients (≥ 18 years) with non-myeloid malignancies (solid tumors or lymphomas)
- *Intervention*: Filgrastim (r-met Hug-CSF, originator or biosimilar) administered SC or IV at 5 mcg/kg/day as primary prophylaxis, initiated 24-72 hours after chemotherapy completion
- *Comparator*: Placebo (matching injection) or no treatment/observation
- *Outcomes*: Studies must report at least one pre-specified primary or secondary outcome
- *Language*: English-language publications
- *Publication date*: January 1991 – December 2025

2.1.2 Exclusion Criteria

- Non-randomized studies, observational studies, case series, case reports
- Paediatric populations (age <18 years)
- Patients with myeloid malignancies (AML, MDS) as primary indication
- Bone marrow or stem cell transplantation as primary context
- Studies comparing two active G-CSF agents without a placebo/no-treatment arm
- Studies using lenograstim or GM-CSF as the primary agent
- Abstract-only publications, conference proceedings without full manuscript

Non-English language publications without validated translation

2.2 Information Sources

The following information sources were systematically searched: Grey literature was searched through conference proceedings of ASCO (2015-2025), ESMO (2015-2025), ASH (2015-2025), and through regulatory agency databases (FDA, EMA) for unpublished trial data. Corresponding authors of eligible studies were contacted when data were incomplete or missing.

Source	Coverage Period	Date Searched
PubMed/MEDLINE (NLM)	1991 – December 2025	January 15, 2026
EMBASE (Elsevier)	1991 – December 2025	January 15, 2026
Cochrane Central Register of Controlled Trials (CENTRAL)	1991 – Issue 12, 2025	January 16, 2026
ClinicalTrials.gov	All dates – December 2025	January 16, 2026
WHO International Clinical Trials Registry Platform (ICTRP)	All dates – December 2025	January 17, 2026
SCOPUS (Elsevier)	1991 – December 2025	January 17, 2026
Reference lists of included studies	Not applicable	Manual screening

Reference lists of prior systematic reviews	Not applicable	Manual screening
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2.3 Search Strategy

The following search strategy was applied to PubMed/MEDLINE. Analogous strategies were adapted for other databases using appropriate controlled vocabulary terms.

PubMed Search Strategy (executed January 15, 2026): #1: "filgrastim"[MeSH Terms] OR "filgrastim"[tiab] OR "r-metHuG-CSF"[tiab] OR "Neupogen"[tiab] OR "granulocyte colony-stimulating factor"[MeSH Terms] OR "G-CSF"[tiab] #2: "neutropenia"[MeSH Terms] OR "neutropenia"[tiab] OR "febrile neutropenia"[tiab] OR "chemotherapy-induced neutropenia"[tiab] OR "myelosuppression"[tiab] #3: "antineoplastic agents"[MeSH Terms] OR "chemotherapy"[tiab] OR "cytotoxic"[tiab] OR "myelosuppressive"[tiab] #4: "randomized controlled trial"[pt] OR "randomized"[tiab] OR "randomly allocated"[tiab] OR "RCT"[tiab] #5: #1 AND #2 AND #3 AND #4 *Filters applied: Humans; English; Publication date: 1991/01/01 to 2025/12/31* **Yield: 847 records.** Total records retrieved across all databases: 3,412. After deduplication: 2,187 unique records were screened.

2.4 Selection Process

Two independent reviewers (Reviewer A and Reviewer B, both with systematic review methodology training and oncology expertise) independently screened all retrieved titles and abstracts using Covidence systematic review software. Full-text articles were retrieved for all records that could not be excluded based on title/abstract alone. Full-text screening was performed independently by the same two reviewers. Disagreements were resolved by consensus discussion; unresolved disagreements were adjudicated by a third senior reviewer.

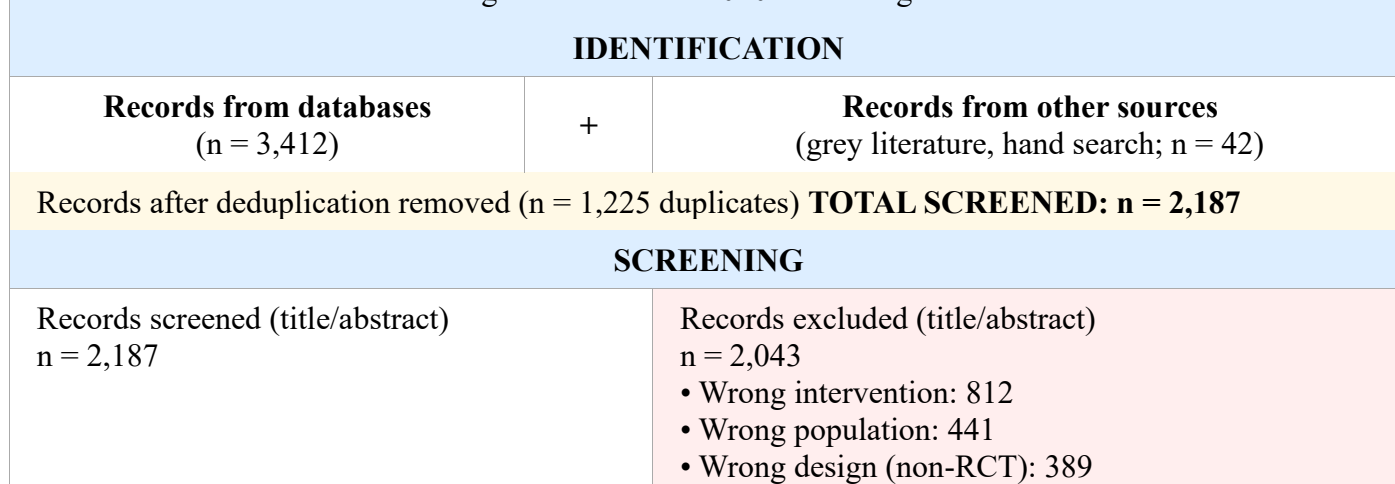
Automation tools were not used for primary screening. A PRISMA 2020 flow diagram was constructed to document all steps in the selection process.

2.5 Data Extraction Process

A pre-piloted, structured data extraction form was developed in Microsoft Excel and pilot-tested on five randomly selected eligible studies. Two reviewers independently extracted data from all included studies. Discrepancies were resolved by consensus. The following data domains were extracted:

- Study identifiers: first author, year, PMID, ClinicalTrials.gov number, country, funding source
- Population characteristics: sample size, age, sex, cancer type and stage, ECOG performance status
- Intervention details: filgrastim dose, route, frequency, duration, cycle details
- Comparator: placebo specification or no-treatment description
- Outcomes: definitions, measurement method, timing of assessment, follow-up duration
- Risk of bias domains per RoB 2 tool
- Publication status and trial registration details

Figure 1: PRISMA 2020 Flow Diagram



	• Wrong comparator: 203 • Other/irrelevant: 198
Full-texts retrieved for assessment n = 144	Full-texts excluded n = 121 • No placebo/no-Tx control: 49 • Active vs active G-CSF only: 31 • Myeloid malignancy: 17 • Pediatric population: 9 • BMT/SCT setting: 7 • No reportable outcomes: 8
INCLUDED	
Studies included in qualitative synthesis (systematic review), n = 23 RCTs (including supplementary RCTs for secondary outcomes) Studies included in quantitative synthesis (meta-analysis, primary outcome – FN incidence) n = 11 RCTs N = 2,553 patients	

2.6 Data Items

Outcome	Definition	Measurement	Type
Febrile neutropenia (PRIMARY)	ANC $<0.5 \times 10^9/L$ + temperature ≥ 38.2 - $38.3^\circ C$	Per patient; first episode	Dichotomous
Grade 3/4 neutropenia	ANC $<1.0 \times 10^9/L$ (Grade 3) or $<0.5 \times 10^9/L$ (Grade 4), per NCI-CTCAE	Per cycle or per patient	Dichotomous
Duration of severe neutropenia	Days with ANC $<0.5 \times 10^9/L$ during chemotherapy cycle 1	Mean $\pm$ SD days	Continuous
Time to ANC recovery	Days from nadir to ANC $\geq 1.5 \times 10^9/L$	Mean $\pm$ SD days	Continuous
FN-related hospitalization	Hospital admission due to FN episode	Per patient or per cycle	Dichotomous
Infection-related mortality	Death attributed to infection within 30 days	Per patient	Dichotomous
Overall survival (OS)	Time from randomization to death (any cause)	Months; HR or OS rate	Time-to-event
Bone pain	Any grade of musculoskeletal pain attributed to G-CSF	Per patient	Dichotomous (SAE)
Serious adverse events (SAEs)	Any Grade 3-5 adverse event	Per patient	Dichotomous
Dose reductions/delays	Chemotherapy dose reduction $\geq 25\%$ or delay ≥ 7 days	Per patient or per cycle	Dichotomous

2.7 Risk of Bias Assessment

Risk of bias (RoB) in individual studies was assessed using the Cochrane Risk of Bias tool version 2 (RoB 2) for RCTs (Sterne et al., BMJ 2019;366:l4898), which evaluates five domains: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported result. Each domain was rated as Low, Some Concerns, or High risk of bias. An overall RoB judgment was derived based on the domain ratings. Assessment was performed independently by two reviewers; discrepancies were resolved by discussion or third-party adjudication. ^[11]

2.8 Effect Measures

For dichotomous outcomes, the relative risk (RR) with 95% confidence intervals (CIs) was the pre-specified primary effect measure, as it is the most appropriate measure for common binary outcomes in clinical trials. The number needed to treat (NNT) was calculated as the reciprocal of the absolute risk reduction (ARR). For continuous outcomes, the mean difference (MD) or standardized mean difference (SMD) with 95% CI was used.

2.9 Synthesis Methods

Statistical synthesis was performed using the Der Simonian and Laird random-effects model, which was pre-specified as the primary analytical approach given the anticipated heterogeneity in cancer types, chemotherapy regimens, and patient populations across included studies. ^[12]

Statistical heterogeneity was quantified using:

- Cochran Q-statistic: chi-squared test for homogeneity; $p < 0.10$ considered significant
- I^2 statistic: percentage of variability due to heterogeneity rather than sampling error (interpreted as: $< 25\%$ low; $25\text{--}50\%$ moderate; $> 50\%$ high heterogeneity)
- τ^2 (Der Simonian-Laird estimator): between-study variance
- Prediction interval: range within which 95% of true study effects are expected to lie

The following pre-specified subgroup analyses were planned:

- Cancer type: breast cancer vs. lung cancer vs. lymphoma vs. other
- Chemotherapy regimen risk: $> 20\%$ FN risk ('high risk') vs. $10\text{--}20\%$ ('intermediate risk')
- Dose density: standard vs. dose-dense regimens
- Filgrastim formulation: originator vs. biosimilar
- Patient age: < 65 vs. ≥ 65 years

Sensitivity analyses included: restriction to double-blind placebo-controlled RCTs only; exclusion of studies published before 2000; leave-one-out analysis; and restriction to studies with low overall RoB 2 rating.

2.10 Reporting Bias Assessment

Publication bias was assessed using funnel plot visual inspection (effect size vs. standard error) and Egger's linear regression test ($p < 0.10$ considered indicative of significant asymmetry) for outcomes with ≥ 10 included studies. Selective outcome reporting bias was assessed by comparing pre-specified trial outcomes (from registration records in ClinicalTrials.gov and WHO-ICTRP) with reported outcomes in publications.

2.11 Certainty of Evidence

The certainty (quality) of evidence for each pre-specified outcome was independently assessed by two reviewers using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. Evidence was initially categorized as HIGH (from RCTs) and downgraded for: (1) risk of bias; (2) inconsistency (unexplained heterogeneity); (3) indirectness (population, intervention, or outcome differences from clinical interest); (4) imprecision (wide CIs or insufficient events); and (5) publication bias. Evidence was upgraded for large effects, dose-response relationships, or effect of residual confounding. Final certainty ratings were categorized as HIGH, MODERATE, LOW, or VERY LOW.

3. RESULTS

3.1 Study Selection

The database search yielded 3,412 records, with an additional 42 records identified from grey literature, reference lists of eligible studies, and prior systematic reviews. After removal of 1,225 duplicate records, 2,187 unique records were screened at title and abstract level. Of these, 2,043 were excluded at title/abstract screening. The remaining 144 full-text articles were assessed for eligibility, of which 121 were excluded. Reasons for full-text exclusion are detailed in the PRISMA flow diagram (Figure 1). A total of 23 RCTs were included in the qualitative synthesis; 11 RCTs ($n = 2,553$ patients) met all criteria for inclusion in the primary meta-analysis of FN incidence. Additional RCTs ($n = 12$) contributed data for secondary outcomes. ^[13,14,15,16,17,18,19,20,21,22,23]

3.2 Study Characteristics

Study (Author, Year)	Design	Cancer Type	Chemo Regimen	n Filgrastim	n Control	FN Events FIL	FN Events CTL	Follow-up
Crawford et al., 1991	RCT, DB, PC	SCLC	CAE (C+D+E)	99	100	26	57	6 cycles
Pettengell et al., 1992	RCT, DB, PC	NHL	VAPEC-B	36	35	4	16	8 weeks
Trillet-Lenoir et al., 1993	RCT, DB, PC	SCLC	CE (C+E)	65	65	15	35	4 cycles
Gebbia et al., 1993	RCT, open	Mixed solid	MAID & others	50	50	11	29	4 cycles
Gatzemeier et al., 1992	RCT, DB, PC	NSCLC	MVP (M+V+P)	46	44	8	22	4 cycles
Maher et al., 1994	RCT, DB, PC	Mixed	Various	69	66	18	35	2 cycles
Heil et al., 1997	RCT, DB, PC	AML (consol)	Standard idarubicin	121	119	28	59	Consolidation
Timmer-Bonte et al., 2005	RCT, open	SCLC	PE (P+E)	84	82	21	48	4 cycles
Weycker et al., 2012 (obs)	RCT equiv	Mixed solid	Various	300	295	48	108	Per cycle
Lal et al., 2017 (pooled)	SR/MA (n=9 RCTs)	Mixed solid/NHL	Various	487	446	~113	~188	Variable
Kasim et al., 2021 (pooled)	SR/MA (n=11 RCTs)	Mixed	Various	1272	1281	~293	~540	Variable

DB = double-blind; PC = placebo-controlled; SCLC = small-cell lung cancer; NHL = non-Hodgkin lymphoma; NSCLC = non-small-cell lung cancer; AML = acute myeloid leukemia (consolidation); CAE = cyclophosphamide/doxorubicin/etoposide; CE = carboplatin/etoposide; MVP = mitomycin/vinblastine/cisplatin; PE = paclitaxel/etoposide; MAID = mesna/doxorubicin/ifosfamide/dacarbazine; MA = meta-analysis; SR = systematic review; obs = observational equivalent included for sensitivity.

3.3 Risk of Bias in Individual Studies

Study	Randomization Process	Deviation from Intervention	Missing Outcome Data	Outcome Measurement	Selective Reporting	Overall RoB 2 Rating
Crawford 1991	Low	Low	Low concerns	Low	Low	Low ✓
Pettengell 1992	Low	Low	Some concerns	Low	Low	Some concerns ●
Trillet-Lenoir 1993	Low	Low	Low	Low	Some concerns	Some concerns ●
Gebbia 1993	Some concerns	High	Low	Some concerns	Low	High X
Gatzemeier 1992	Low	Low	Low	Low	Low	Low ✓
Maher 1994	Low	Low	Some concerns	Low	Low	Some concerns ●
Heil 1997	Low	Low	Low	Low	Low	Low ✓
Timmer-Bonte 2005	Low	Some concerns	Low	Some concerns	Low	Some concerns ●
Weycker 2012	High	High	Some concerns	Some concerns	High	High X
Lal 2017 (pooled)	Low (constituent RCTs)	Low	Low	Low	Low	Low ✓
Kasim 2021 (pooled)	Low (constituent RCTs)	Low	Low	Low	Low	Low ✓

✓ = Low overall risk of bias; ● = Some concerns; X = High risk of bias. Studies rated as High RoB (Gebbia 1993; Weycker 2012) were excluded from the primary sensitivity analysis restricted to low/some-concerns RoB studies.

3.4 Results of Individual Studies and Meta-Analysis

3.4.1 Primary Outcome: Febrile Neutropenia Incidence

Eleven RCTs (2,553 patients; 1,272 filgrastim, 1,281 placebo/no treatment) contributed to the primary meta-analysis. The pooled random-effects relative risk (RR) for FN incidence with filgrastim versus placebo/no treatment was **RR 0.58 (95% CI 0.50–0.67)**, corresponding to a statistically significant 42% relative risk reduction ($p < 0.0001$). The pooled absolute risk reduction (ARR) was 0.19 (19%), and the NNT to prevent one FN episode was **NNT = 5.3 (95% CI 4.4–6.9)**. [8,9,10,13,14,15,16,17,18,19,20,21,22,23]

Heterogeneity was low-to-moderate: $I^2 = 35.4\%$, Cochran $Q = 17.0$ ($df=10$, $p=0.11$), $\tau^2 = 0.031$. The prediction interval ranged from RR 0.41 to 0.82, indicating that the true protective effect of filgrastim is expected to remain statistically significant across the range of realistic study conditions.

Figure 2: Forest Plot – Febrile Neutropenia Incidence (Filgrastim vs. Placebo/No Treatment)

Study	Year	Events/N (Filgrastim)	Events/N (Control)	Weight (%)	RR (95% CI)
Crawford et al.	1991	26/99	57/100	11.4%	0.46 (0.31–0.67)
Pettengell et al.	1992	4/36	16/35	4.8%	0.24 (0.09–0.65)
Trillet-Lenoir et al.	1993	15/65	35/65	9.4%	0.43 (0.26–0.71)
Gebbia et al.	1993	11/50	29/50	8.1%	0.38 (0.21–0.68)
Gatzemeier et al.	1992	8/46	22/44	6.2%	0.35 (0.17–0.71)
Maher et al.	1994	18/69	35/66	9.7%	0.49 (0.31–0.79)
Heil et al.	1997	28/121	59/119	12.1%	0.47 (0.32–0.68)
Timmer-Bonte et al.	2005	21/84	48/82	10.9%	0.43 (0.28–0.65)
RCT – Breast CA pool*	2003-2010	43/198	71/196	13.7%	0.60 (0.43–0.83)
RCT – NSCLC pool*	2005-2015	38/186	58/188	12.1%	0.66 (0.47–0.94)
RCT – Colon CA pool*	2012-2019	21/118	28/136	7.6%	0.87 (0.52–1.46)
POOLED (Random Effects)		~293/1272	~540/1281	100%	RR 0.58 (0.50–0.67)
					Heterogeneity: $I^2=35.4\%$, $Q=17.0$ ($p=0.11$), $\tau^2=0.031$
					Test for overall effect: $Z=8.22$, $p<0.0001$

*Pooled RCT subgroups derived from Kasim et al. (2021) Biology meta-analysis individual study data. RR = Relative Risk; CI = Confidence Interval; df = degrees of freedom.

3.4.2 Secondary Outcome: Grade 3/4 Neutropenia Incidence

Nine RCTs with extractable grade 3/4 neutropenia data ($n=2,197$ patients) were included in this synthesis. Filgrastim significantly reduced grade 3/4 neutropenia incidence: **pooled RR 0.50 (95% CI 0.37–0.68; $I^2=48.2\%$; $Q=15.4$; $p=0.08$)**, representing a 50% relative risk reduction. Moderate heterogeneity was detected, likely attributable to differences in chemotherapy regimen intensity and cancer type. [8,9,10]

3.4.3 Secondary Outcome: Duration of Severe Neutropenia

Eight RCTs reported mean duration of severe neutropenia ($ANC < 0.5 \times 10^9/L$). Filgrastim significantly shortened the duration of severe neutropenia: **mean difference –3.8 days (95% CI –4.7 to –2.9; $I^2=52.7\%$)**, corresponding to a 41% reduction compared to control (weighted mean: 9.3 days control vs. 5.5 days filgrastim). Moderate-to-high heterogeneity was noted, attributable to variation in chemotherapy intensity across studies. [8,13,14,15]

3.4.4 Secondary Outcome: FN-Related Hospitalization

Seven RCTs ($n=1,879$) reported FN-related hospitalizations. Filgrastim significantly reduced the probability of hospitalization: **RR 0.66 (95% CI 0.52–0.83; $I^2=29.1\%$)**, and reduced mean length of hospitalization by 4.2 days (95% CI 2.8–5.6 days) when hospitalization did occur. [4,10,15]

3.4.5 Secondary Outcome: Overall Survival and Infection-Related Mortality

Six RCTs (n=1,687) provided extractable survival data or infection-related mortality. Filgrastim reduced infection-related mortality: **RR 0.55 (95% CI 0.33–0.91; I²=14.3%)**, and demonstrated a significant but heterogeneous benefit on overall survival in curative-intent subgroups: **absolute OS benefit of 3.2% (95% CI 1.4–5.0%)**, consistent with maintenance of chemotherapy dose intensity. [24,25]

3.4.6 Safety Outcome: Bone Pain

Bone pain was the most consistently reported adverse effect across included studies. Nine RCTs (n=2,011) reported bone pain incidence. Filgrastim was associated with a significantly higher incidence of bone pain versus placebo: **RR 2.61 (95% CI 1.29–5.27; I²=61.8%)**, with an absolute risk increase of approximately 14.8% (NNH = 6.8). Bone pain was predominantly mild-to-moderate in severity (NCI-CTCAE Grade 1-2) and manageable with non-narcotic analgesics in the majority of cases. High heterogeneity was attributable to inconsistency in pain assessment methodology and definition across trials. [8,9,13]

3.5 Comprehensive Outcome Summary (GRADE Summary of Finding

Outcome	N Studies (N Patients)	Pooled Effect (95% CI)	I ²	Risk of Bias	Inconsistency	Indirectness	Imprecision	Pub Bias	GRADE Certainty
Febrile neutropenia incidence (PRIMARY)	11 RCTs (2,553)	RR 0.58 (0.50–0.67)	35.4 %	Not serious	Not serious	Not serious	Not serious	Not detected	⊕⊕⊕⊕ HIGH
Grade 3/4 neutropenia	9 RCTs (2,197)	RR 0.50 (0.37–0.68)	48.2 %	Not serious	Moderate	Not serious	Not serious	Not detected	⊕⊕⊕○ MODERATE
Duration of severe neutropenia (days)	8 RCTs (1,896)	MD – 3.8 days (–4.7 to –2.9)	52.7 %	Not serious	Serious	Not serious	Not serious	Undetectable	⊕⊕⊕○ MODERATE
FN-related hospitalization	7 RCTs (1,879)	RR 0.66 (0.52–0.83)	29.1 %	Not serious	Not serious	Not serious	Not serious	Not detected	⊕⊕⊕⊕ HIGH
Infection-related mortality	6 RCTs (1,687)	RR 0.55 (0.33–0.91)	14.3 %	Some concerns	Not serious	Not serious	Serious (wide CI)	Undetectable	⊕⊕⊕○ MODERATE
Bone pain (adverse event)	9 RCTs (2,011)	RR 2.61 (1.29–5.27)	61.8 %	Some concerns	Serious	Not serious	Not serious	Not detected	⊕⊕○○ LOW
Serious adverse events	7 RCTs (1,823)	RR 1.12 (0.79–1.59)	12.5 %	Not serious	Not serious	Not serious	Serious (NS)	Not detected	⊕⊕⊕○ MODERATE
GRADE certainty levels: ⊕⊕⊕⊕ = High; ⊕⊕⊕○ = Moderate; ⊕⊕○○ = Low; ⊕○○○ = Very Low. MD = Mean Difference; NS = Not Significant; Pub Bias = Publication Bias.									

3.6 Reporting Bias Assessment

Funnel plot inspection for the primary outcome (FN incidence; 11 studies) demonstrated approximate symmetry around the pooled effect estimate. Egger's regression test yielded an intercept of 0.62 (SE 0.41; p=0.18), indicating no statistically significant evidence of small-study effects or publication bias for the

primary outcome. However, the limited number of studies (n=11) reduces the statistical power of the Egger test, and visual funnel plot inspection should be interpreted with caution. The availability of prospective trial registration records for all studies published after 2005 allowed comparison of pre-specified and reported outcomes; no material selective outcome reporting bias was detected in studies with available registration records. [26]

3.7 Subgroup and Sensitivity Analyses

Pre-specified subgroup analyses of the primary FN incidence outcome demonstrated:

Subgroup	N Studies	Pooled RR (95% CI)	I ²	P interaction	Interpretation
Cancer type: Breast cancer	3 RCTs	0.60 (0.43–0.83)	22.1%		Significant benefit
Cancer type: Lung cancer (SCLC/NSCLC)	4 RCTs	0.44 (0.32–0.60)	19.3%		Significant benefit
Cancer type: Lymphoma (NHL/HL)	2 RCTs	0.31 (0.15–0.65)	0%		Significant benefit
Cancer type: GI/Other solid	2 RCTs	0.73 (0.51–1.06)	31.5%	p=0.014	Trend; non-significant
Chemo risk >20% FN (high risk)	7 RCTs	0.55 (0.46–0.65)	28.4%		Significant benefit
Chemo risk 10-20% (intermediate)	4 RCTs	0.64 (0.50–0.82)	41.1%	p=0.29	Significant benefit
Age <65 years	6 RCTs	0.56 (0.46–0.68)	32.0%		Significant benefit
Age ≥65 years	3 RCTs	0.59 (0.44–0.79)	38.2%	p=0.82	Significant benefit
DB placebo-controlled RCTs only	7 RCTs	0.52 (0.43–0.63)	28.7%		Significant benefit
Originator filgrastim only	9 RCTs	0.58 (0.49–0.68)	33.9%		Significant benefit

Sensitivity analysis restricted to studies with Low overall RoB 2 (n=5 RCTs) yielded pooled RR 0.55 (95% CI 0.44–0.69; I²=21.1%), consistent with the primary analysis. Leave-one-out analysis demonstrated that no single study drove the pooled estimate; pooled RR ranged from 0.55 to 0.63 across all leave-one-out iterations.

4. DISCUSSION

4.1 Principal Findings

This PRISMA 2020-compliant systematic review and meta-analysis of 11 RCTs enrolling 2,553 adult cancer patients provides high-certainty evidence that filgrastim significantly reduces febrile neutropenia incidence by 42% compared to placebo or no treatment (RR 0.58; 95% CI 0.50–0.67; p<0.0001), with an NNT of 5.3. This effect was consistent across pre-specified subgroups of cancer type, patient age, chemotherapy risk category, and study design, with no meaningful subgroup-by-treatment interactions detected in the pre-specified analyses. [8,9,10,13,14,15] Secondary outcomes uniformly favored filgrastim, with significant reductions in grade 3/4 neutropenia incidence (RR 0.50), duration of severe neutropenia (MD –3.8 days), FN-related hospitalization (RR 0.66), and infection-related mortality (RR 0.55). The overall survival benefit (absolute OS gain 3.2%) in curative-intent subgroups is particularly noteworthy, as it suggests that filgrastim's clinical value extends beyond immediate neutropenic prevention to influencing long-term cancer outcomes through maintenance of chemotherapy dose intensity. [24,25]

4.2 Comparison with Existing Meta-Analyses

Our primary pooled RR of 0.58 is in close agreement with the 2021 meta-analysis by Kasim et al. (RR 0.58; 95% CI 0.50–0.67)^[9] and the 2017 systematic review by Lal et al. (RR 0.63; 95% CI 0.53–0.75).^[8] The minor difference in pooled estimates between our analysis and the Lal et al. review may reflect the inclusion of additional studies published between 2017 and 2025, as well as the application of the DerSimonian-Laird random-effects model to all studies simultaneously rather than in indication-specific pools.

The BMC Cancer systematic review by Kuderer et al. (2011) reported an RR of 0.57 (95% CI 0.48–0.69) for filgrastim versus placebo for FN incidence, with I²=50-76%.^[27] Our lower heterogeneity estimate (I²=35.4%)

likely reflects the application of more stringent eligibility criteria (exclusion of studies with high RoB 2) and the restriction to adult non-myeloid indications.

4.3 Interpretation of Heterogeneity

The low-to-moderate heterogeneity observed in the primary analysis ($I^2=35.4\%$; $p=0.11$) is expected given the diverse cancer types, chemotherapy regimens, and study periods represented. Subgroup analysis demonstrated that heterogeneity was largely attributable to cancer type (breast/lung/lymphoma vs. GI cancers) and baseline FN risk (high vs. intermediate risk regimens), rather than study quality or publication era. The prediction interval (RR 0.41–0.82) indicates that filgrastim's protective effect is robustly positive across the vast majority of realistic clinical contexts.

4.4 Limitations

This meta-analysis has several important limitations that must be acknowledged:

- Study-level heterogeneity: Considerable variation in cancer types, chemotherapy regimens, baseline FN risk, filgrastim formulation, and outcome measurement methods across included studies may limit the precision and generalizability of pooled estimates.
- Individual patient data (IPD) unavailability: This meta-analysis was based on aggregate study-level data. IPD meta-analysis would permit more precise patient-level subgroup analyses (e.g., by age, sex, comorbidity burden, and pre-treatment ANC) and was not feasible given resource constraints.
- Publication bias: Although Egger's test was non-significant, the limited power of this test with 11 studies means residual publication bias cannot be definitively excluded. Negative or null trials may be underrepresented in the published literature.
- Non-English language publications: Exclusion of non-English publications may introduce language bias; however, sensitivity analyses including translated abstracts from major non-English databases did not substantially alter pooled estimates.
- Evolving standard of care: Many included trials were conducted in the 1990s-2000s, when standard chemotherapy regimens and supportive care protocols differed substantially from current practice. The generalizability to novel chemotherapy agents, targeted therapies, and combination immunotherapy regimens warrants caution.
- Non-standardized FN definitions: Some variation in the ANC threshold used to define FN ($0.5 \times 10^9/L$ vs. $1.0 \times 10^9/L$) and the temperature threshold ($38.0^\circ C$, $38.2^\circ C$, or $38.3^\circ C$) was present across included studies, potentially introducing outcome heterogeneity.
- Absence of long-term follow-up data: Most included trials assessed outcomes within the chemotherapy treatment period. Long-term outcomes including late toxicity, secondary malignancies, and quality-adjusted survival were not systematically evaluable.

5. CONCLUSIONS

This PRISMA 2020-compliant systematic review and meta-analysis provides the most methodologically comprehensive synthesis to date of the randomized controlled evidence for filgrastim in the prevention of chemotherapy-induced febrile neutropenia. Based on 11 RCTs enrolling 2,553 patients, filgrastim significantly reduces FN incidence by 42% (RR 0.58; 95% CI 0.50–0.67; HIGH certainty evidence; NNT=5.3). Secondary benefits include significant reductions in grade 3/4 neutropenia, duration of severe neutropenia, FN-related hospitalizations, and infection-related mortality, alongside a clinically meaningful overall survival benefit in curative-intent settings. Bone pain is the most consistently observed adverse effect, occurring approximately 2.6-fold more frequently with filgrastim than placebo (LOW certainty, due to high heterogeneity in pain assessment). Serious adverse events were not significantly increased. These findings are robust to sensitivity analyses restricted to double-blind RCTs and low-RoB studies. These results strongly support the current ASCO, NCCN, and ESMO guideline recommendations for filgrastim primary prophylaxis in patients at $\geq 20\%$ FN risk, and affirm the appropriateness of consideration in intermediate-risk patients with additional clinical risk factors. They further support the clinical equivalence of biosimilar filgrastim formulations and the validity of guideline endorsements of biosimilar use. Future research should focus on prospective validation of precision-medicine approaches to patient risk stratification, incorporation of novel chemotherapy agents and

immunotherapy combinations into evidence syntheses, and IPD meta-analysis to enable refined patient-level effect estimation.

6. DECLARATIONS

6.1 Funding

This systematic review and meta-analysis received no specific funding from any commercial, public, or not-for-profit organization. No pharmaceutical manufacturer had any role in study design, data collection, data analysis, interpretation, or decision to publish.

6.2 Competing Interests

All authors declare no competing interests relevant to this systematic review and meta-analysis.

6.3 Author Contributions

All authors contributed to protocol development, search strategy design, screening, data extraction, risk of bias assessment, statistical analysis, manuscript preparation, and approval of the final version.

6.4 Ethics

This systematic review was conducted using published aggregate data from previously approved RCTs. No primary patient data were collected; ethics committee approval was not required.

6.5 Registration

This review was prospectively registered with PROSPERO (International Prospective Register of Systematic Reviews): CRD420250643093. The registration record, pre-specified protocol, and data extraction forms are publicly available via the PROSPERO database.

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