RESEARCH PAPER

Disproportionality Signal Analysis of Cardiac Adverse Events Associated with Filgrastim and Pegfilgrastim using EudraVigilance and FAERS

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ABSTRACT

Background: Filgrastim and pegfilgrastim granulocyte colony-stimulating factors (G-CSFs) are widely used in oncology, yet their cardiac safety profiles need a systemic pharmacovigilance evaluation.

Objectives: To detect and compare cardiac adverse-event reporting signals for filgrastim and pegfilgrastim biosimilars using EudraVigilance and FAERS.

Methods: Disproportionality analyses were conducted from market authorization through 30 June 2024 in reports where filgrastim or pegfilgrastim biosimilars were recorded as suspect drugs and at least one Preferred Term (PT) under the System Organ Class (SOC) "Cardiac disorders". The top 30 cardiac PTs (highest reporting frequency within each database) were evaluated. Metrics included ROR with 95% confidence interval, PRR, χ^2, and IC_{025}.

Results: EudraVigilance included 953 cardiac reports (filgrastim n=583; pegfilgrastim n=370) and identified three strong statistical signals: filgrastim-cardiotoxicity (ROR 28.32; 95% CI 1.710-469.014), filgrastim-pericarditis (ROR 2.49; 95% CI 1.005-6.179), and pegfilgrastim-cardiac disorder (ROR 2.52; 95% CI 1.346-4.705). FAERS included 2,020 drug-associated cardiac reports after exclusions and identified 12 strong signals. Concordant strong statistical signals across both databases were filgrastim-cardiotoxicity, filgrastim-pericarditis, and pegfilgrastim-cardiac disorder.

Conclusions: Dual-database signal detection identified three strong statistical signals within cardiac disorders, supporting prioritization for further validation in longitudinal healthcare datasets.

Keywords: Filgrastim; pegfilgrastim; pharmacovigilance; disproportionality analysis; EudraVigilance; FAERS; cardiac disorders.

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INTRODUCTION

Granulocyte colony-stimulating factors (G-CSFs) are widely used in supportive oncology care for the prevention and management of chemotherapy-induced neutropenia and febrile neutropenia, reducing infection-related complications and supporting maintenance of planned chemotherapy dose intensity [1,2]. Continued post-marketing evaluation is important to identify uncommon but clinically meaningful adverse events that may not be fully characterized during pre-approval development, particularly in heterogeneous populations with comorbidity and polypharmacy.

Filgrastim and pegfilgrastim differ in duration of action and dosing frequency, which may influence exposure patterns across chemotherapy cycles. Although clinical trials establish efficacy and characterize common adverse reactions, they may be underpowered to detect rare, delayed, or population-specific events. Therefore, spontaneous reporting systems remain important for post-marketing pharmacovigilance. In the United States, the FDA Adverse Event Reporting System (FAERS) is a major resource for safety monitoring of medicinal products and biologics and supports hypothesis generation from spontaneous reports [3,4]. In Europe, the EMA's EudraVigilance (EV) supports regulatory signal detection and pharmacovigilance evaluation [5,6].

Disproportionality analysis is widely applied within spontaneous reporting systems to identify drug-event pairs reported more frequently than expected relative to a defined background. Such findings represent statistical associations

rather than incidence and do not establish causality; interpretation must account for limitations including under-reporting, missing data, reporting bias, and confounding by indication [7,8]. As adverse events in FAERS and EudraVigilance are encoded using standardized MedDRA terminology, outcomes can be consistently defined at the SOC and PT levels to support cross-database comparability [9]. Disproportionality methods have been widely applied in FAERS across diverse drug classes [10,11], including comparative evaluations in infectious disease pharmacotherapy [12].

Cardiac adverse events are clinically relevant in G-CSF-exposed populations because oncology patients frequently have baseline cardiovascular risk factors and may receive concomitant therapies with potential cardiovascular effects. Biological and clinical evidence suggests that G-CSF can influence inflammatory and thrombotic pathways relevant to cardiovascular vulnerability, and higher endogenous G-CSF levels have been associated with subsequent cardiovascular events in stable coronary artery disease [13]. Vascular inflammatory reactions such as G-CSF-associated aortitis have been described across case reports and observational analyses [14,15]. Additional case series and literature review further support this cardio-inflammatory context for safety monitoring [16,17]. Cardiac safety signal analyses using post-marketing reports from EMA and WHO databases have been used to characterize cardiac reporting profiles for other drug classes, providing methodological precedent for cardiac-focused pharmacovigilance investigations [18].

Prior pharmacovigilance research has demonstrated the feasibility of comparative assessment of filgrastim and pegfilgrastim reporting profiles within individual spontaneous reporting systems, including EudraVigilance-based comparative analyses of filgrastim versus pegfilgrastim [19] and FAERS-based disproportionality evaluations of pegylated versus non-pegylated G-CSF products [20]. In addition, discussions regarding the comparability of biosimilar and reference pegfilgrastim reporting profiles underscore ongoing clinical interest in comparative G-CSF safety assessment [21]. However, focused evaluations restricted to cardiac outcomes and explicitly assessing whether strong disproportionality signals are consistent across both FAERS and EudraVigilance, while restricting exposure to biosimilar products, remain limited.

Accordingly, the present study was designed to (i) identify cardiac safety signals reported with filgrastim and pegfilgrastim biosimilars using EudraVigilance and FAERS, (ii) compare the cardiac safety signal profiles of the two agents within each database, and (iii) assess whether identified strong disproportionality signals are concordant across databases or appear database-specific under the prespecified top-30 PT framework, thereby supporting prioritization for pharmacovigilance monitoring and informing future validation studies [22].

METHODS

Study design

We conducted a retrospective pharmacovigilance disproportionality study using spontaneous adverse event reports from FAERS and EudraVigilance from marketing authorization through 30 June 2024. The analysis was performed at the MedDRA Preferred Term (PT) level within the System Organ Class (SOC) "Cardiac disorders". Reporting and interpretation were aligned with recommended methodological standards for disproportionality analyses using ICSR data [7,8].

Data sources

FAERS (FDA)

FAERS is the U.S. FDA's spontaneous reporting database for post-marketing safety surveillance of drugs and therapeutic biological products and contains ICSRs submitted by healthcare professionals, consumers, and manufacturers [3]. Resources such as the FAERS Public Dashboard support signal exploration and hypothesis generation [4].

EudraVigilance (EMA)

EudraVigilance is the EMA's system for collecting and analyzing suspected adverse reaction reports within the European regulatory framework and supports pharmacovigilance signal detection and assessment [5,6]. EMA documentation describing access to EudraVigilance data and electronic reporting procedures is available [23,24].

Data access and extraction

Data were obtained from FAERS and EudraVigilance for the prespecified study window (marketing authorization through 30 June 2024). Records were filtered to include suspected biosimilar exposures and MedDRA SOC "Cardiac disorders," and then curated for analysis at the Preferred Term level. All analyses were performed after removing the duplicate case reports from generated line listings.

Coding terminology

Adverse events were defined using MedDRA hierarchical terminology [9]. Events were restricted to SOC "Cardiac disorders" and evaluated at the PT level to support standardized outcome definition and cross-database comparability. MedDRA coding reflected the database-provided version available at the time of data extraction.

Drug exposure definition (biosimilars)

The drugs of interest were filgrastim and pegfilgrastim. Reports were included only when the recorded product corresponded to a filgrastim biosimilar or pegfilgrastim biosimilar (based on the product/brand name and drug role fields available in each database); reference products were excluded. Included biosimilar products were mapped to the active ingredient (filgrastim or pegfilgrastim) for analysis. Where role coding was available, exposures were defined when the biosimilar product was reported as a suspect drug (primary or secondary suspect, where applicable). Reports lacking sufficient product information to classify biosimilar versus reference were excluded to minimize exposure misclassification.

Case definition and event selection

Cases were defined as reports containing at least one PT coded under MedDRA SOC "Cardiac disorders" and including filgrastim or pegfilgrastim biosimilars as defined above. Event selection followed a prespecified approach: within SOC "Cardiac disorders", the top 30 PTs were selected based on the highest report frequency in each database within the extracted cardiac SOC dataset defined by reports containing either study drug, and disproportionality metrics were computed for this PT set (with co-exposed reports excluded in FAERS for 2×2 construction, as described below). This frequency-based restriction was used to improve estimate stability and interpretability in sparse spontaneous reporting data; rarer cardiac PTs outside the top-30 set were not evaluated.

FAERS duplicate handling and basic standardization

FAERS includes follow-up and duplicate submissions. Duplicate handling was performed at the case level using standard FAERS practice: when multiple reports shared the same CASEID, the record with the most recent FDA receipt date was retained; if receipt dates were identical, the record with the highest PRIMARYID was retained. Reports listed as deleted/invalid in the FAERS "DELETED" file were excluded. Drug name variants were standardized to active ingredient prior to analysis.

Descriptive variables

For each database and drug, we summarized available ICSR characteristics: age group, sex, seriousness classification, reported outcome (fatal vs other), reporter type, and report origin region/country (where available and interpretable). Missing or unspecified fields were retained and reported as "unknown/not specified" as provided in source data.

Disproportionality analysis

Disproportionality was assessed at the report level for each drug–event pair, where the target drug (D) was filgrastim or pegfilgrastim and the target event (E) was a cardiac Preferred Term (PT). Analyses were conducted within the extracted SOC “Cardiac disorders” analytic set containing reports with either study drug (within-class case–case comparative reporting design). Accordingly, estimates compare the relative distribution of specific cardiac PTs between the two study drugs and do not represent disproportionality versus the full database background.

For each (D, E) pair, the report-level 2×2 table was constructed as shown in Table 1, and Reporting odds ratio (ROR; 95% confidence interval), proportional reporting ratio (PRR), chi-square (χ^2), and the information component (IC) with its lower 95% credibility bound (IC_{025}) were computed from the table. When any cell count equalled zero, a Haldane–Anscombe continuity correction (+0.5 to all cells) was applied before ratios and confidence intervals were calculated. In FAERS, reports listing both study drugs were excluded before 2×2 construction to preserve a mutually exclusive comparator structure.

Table 1 Report-level 2×2 contingency table used for disproportionality calculations [25]

	Target PT ‘E’ present	Target PT ‘E’ absent*	Total
Target drug ‘D’ present	a	b	a + b
Comparator drug (not ‘D’)	c	d	c + d
Total	a + c	b + d	a + b + c + d

*PT ‘E’ absent indicates the presence of other cardiac PT(s) within SOC “Cardiac disorders,” not the absence of cardiac events.

*“not D” refers to the comparator study drug within the case–case analytic set; in FAERS, co-exposed reports listing both study drugs were excluded prior to 2×2 construction.

Signal definition and tiering

Signals were classified using a prespecified multi-criterion framework based on disproportionality measures derived from the report-level 2×2 table (Table 1). Signal strength was determined using statistical thresholds applied to multiple disproportionality metrics, as summarized in Table 2.

Table 2 Disproportionality measures and signal detection criteria [18, 25, 26, 27, 28]

Component	Formula	Signal criterion

Ncomb (a)	Minimum count of 3	a ≥ 3
ROR (95% CI)	(a/c)/(b/d); 95% CI from ln (ROR) ± 1.96×SE. Continuity correction (+0.5 to all cells) applied if any cell was zero.	ROR ≥ 1; lower 95% CI > 1
PRR	[a/(a+b)] / [c/(c+d)]	PRR ≥ 2
χ^2	[(ad-bc)2(a+b+c+d)]/[(a+b)(c+d)(a+c)(b+d)]	$\chi^2 \geq 4$
IC_{025}	Log2 [P (x,y)]/[P(x)*P (y)]	$IC_{025} > 0$

Strong statistical signal (Meets all criteria): a ≥ 3, PRR ≥ 2, lower 95% CI of ROR > 1, $\chi^2 \geq 4$, $IC_{025} > 0$): Signals with high statistical association (screening level).

Suggestive statistical signal (Meets ≥3 of the above criteria): Potential statistical association; more scientific evidence, further monitoring/follow-up recommended.

Cross-database comparison

Signal detection was conducted separately in FAERS and EudraVigilance. PT-level findings were compared to identify: (i) concordant strong signals (strong in both databases), and (ii) strong signals identified in one database that did not meet robust criteria in the other database. Because the PT set was selected as the database-specific top 30 PTs, some drug–PT pairs may fall outside the other database's prespecified PT set; when this occurred, it was explicitly described as "not evaluated" in cross-database summaries. Accordingly, cross-database non-concordance should not be interpreted as evidence of absence of the event in the other region.

Study workflow and dataset construction

A structured workflow was applied to both databases, including drug identification, restriction to cardiac SOC/PTs, selection of top PTs, computation of disproportionality metrics, signal tiering, and cross-database comparison (Fig. 1).

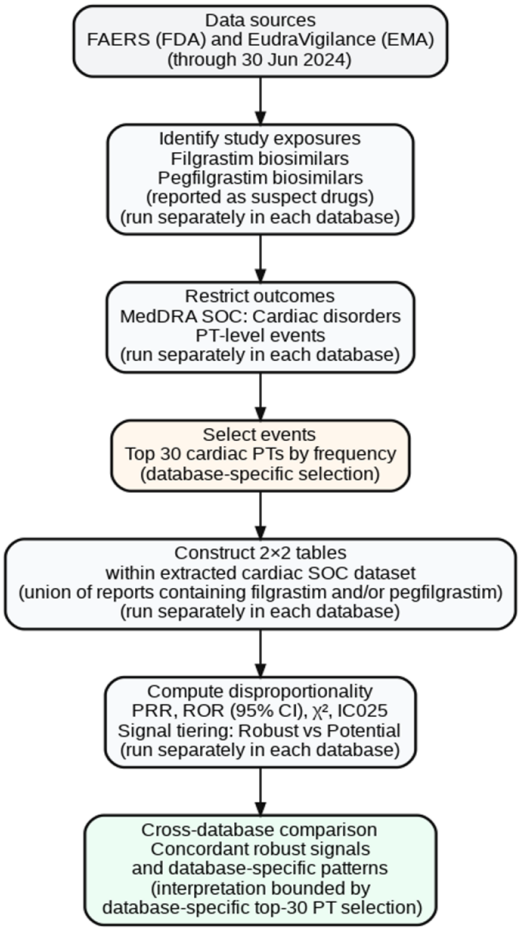

Fig. 1 Study workflow and dataset construction for EudraVigilance and FAERS

Software and reproducibility

Data curation and calculations were performed using Microsoft Excel for the finalized outputs, with consistency checks performed where required using statistical scripting. Tables and figures were generated directly from the finalized descriptive summaries and disproportionality calculations. The analysis uses publicly accessible, de-identified data; therefore, ethics committee approval and informed consent were not required.

RESULTS

Case identification and dataset composition

From market authorization through 30 June 2024, cardiac-related reports associated with filgrastim and pegfilgrastim biosimilars were retrieved from EudraVigilance and FAERS. The EudraVigilance cardiac dataset comprised 953 reports, including 583 reports for filgrastim (61.18%) and 370 reports for pegfilgrastim (38.82%). In FAERS, drug-associated cardiac report counts were 1,092 for filgrastim (52.02%) and 1,007 for pegfilgrastim (47.98%), totaling 2,099 reports. For FAERS disproportionality calculations, the analytic denominator was 2,020 reports, indicating overlap of reports listing both products (overlap = 79 reports, derived from 1,092 + 1,007 - 2,020). This analytic denominator was used consistently for FAERS Ncomb/PRR/ROR/χ^2/IC025 computations. In the extracted EudraVigilance dataset, filgrastim and pegfilgrastim report counts were mutually exclusive (583 + 370 = 953).

Characterization of cardiac reports

EudraVigilance

All EudraVigilance cardiac reports were classified as serious (953/953; 100%) (Table 3). Fatal outcomes were reported more frequently for filgrastim (206/583; 35.33%) than for pegfilgrastim (66/370; 17.84%), corresponding to an overall fatal outcome proportion of 272/953 (28.54%). The age distribution indicated that adults aged 18-64 years accounted for 442/953 (46.38%), and patients aged 65-85 years accounted for 253/953 (26.55%); age was not specified in 200/953 (20.99%). Pediatric reports were uncommon, with the combined 0–17-year groups accounting for 47/953 (4.93%).

Sex distribution differed by product. Male sex was reported in 287/583 (49.23%) of filgrastim-associated reports and 225/370 (60.81%) of pegfilgrastim-associated reports, while sex was unknown/not specified in 63/583 (10.81%) and 19/370 (5.14%), respectively. Regarding report origin, reports were more frequently recorded as originating from non-EEA regions (excluding India) (538/953; 56.45%) than from the EEA (411/953; 43.13%), and reports from India accounted for 4/953 (0.42%).

Table 3 Descriptive characteristics of cardiac reports in EudraVigilance

Characteristic	Category	Filgrastim, n (%)	Pegfilgrastim, n (%)	Total, n (%)
Age group (years)	0-1 month	3 (0.51)	0 (0.00)	3 (0.31)
	2 months-2 years	10 (1.72)	0 (0.00)	10 (1.05)
	3-11 years	16 (2.74)	1 (0.27)	17 (1.78)
	12-17 years	14 (2.40)	3 (0.81)	17 (1.78)
	18-64 years	283 (48.54)	159 (42.97)	442 (46.38)
	65-85 years	143 (24.53)	110 (29.73)	253 (26.55)
	>85 years	6 (1.03)	5 (1.35)	11 (1.15)
	Not specified	108 (18.52)	92 (24.86)	200 (20.99)
Sex	Male	287 (49.23)	225 (60.81)	512 (53.73)
	Female	233 (39.97)	126 (34.05)	359 (37.67)
	Unknown / Not specified	63 (10.81)	19 (5.14)	82 (8.60)
Case seriousness	Serious	583 (100.00)	370 (100.00)	953 (100.00)
	Non-serious	0 (0.00)	0 (0.00)	0 (0.00)
Co-suspect drugs	Not assessed	-	-	-
Concomitant drugs	Present	312 (53.52)	210 (56.76)	522 (54.77)
	Not reported	271 (46.48)	160 (43.24)	431 (45.23)
Reporter type	Health professional	566 (97.08)	333 (90.00)	899 (94.33)
	Consumer / non-health professional	22 (3.77)	37 (10.00)	59 (6.19)
	Unknown	5 (0.86)	0 (0.00)	5 (0.52)

Region of report	EEA	253 (43.40)	158 (42.70)	411 (43.13)
	Non-EEA (excluding India)	327 (56.09)	211 (57.03)	538 (56.45)
	India	3 (0.51)	1 (0.27)	4 (0.42)
Outcome	Fatal	206 (35.33)	66 (17.84)	272 (28.54)
	Other outcomes	377 (64.67)	304 (82.16)	681 (71.46)

Note: Percentages are calculated using drug-specific denominators (filgrastim n=583; pegfilgrastim n=370).

FAERS

In FAERS, most cardiac reports were classified as serious: 1,069/1,092 (97.89%) for filgrastim and 947/1,007 (94.04%) for pegfilgrastim, yielding an overall serious proportion of 2,016/2,099 (96.05%) (Table 4). Fatal outcomes were reported in 397/1,092 (36.36%) of filgrastim-associated reports and 199/1,007 (19.76%) of pegfilgrastim-associated reports, corresponding to an overall fatal outcome proportion of 596/2,099 (28.39%).

Adults aged 18-64 years accounted for 773/2,099 (36.83%), and patients aged >85 years accounted for 405/2,099 (19.29%); age was not specified in 698/2,099 (33.25%) reports. Female sex was reported in 577/1,007 (57.30%) of pegfilgrastim-associated reports compared with 436/1,092 (39.93%) of filgrastim-associated reports. Sex was unknown/not specified in 279/1,092 (25.55%) of filgrastim reports and 118/1,007 (11.72%) of pegfilgrastim reports. Report origin was recorded as non-United States (excluding India) in 1,294/2,099 (61.65%), United States in 637/2,099 (30.35%), unknown in 159/2,099 (7.58%), and India in 9/2,099 (0.43%). (Fig. 2)

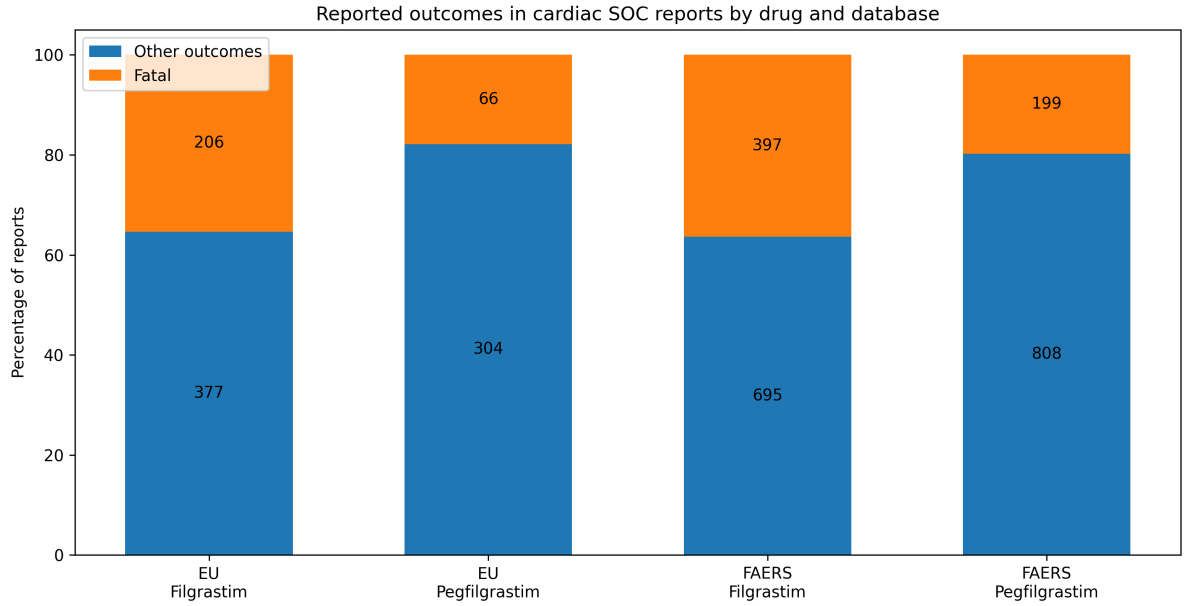

Fig. 2 Reported outcomes (fatal vs other) in cardiac SOC reports by drug and database. Values inside bars are counts

Table 4 Descriptive characteristics of cardiac reports in FAERS

Characteristic	Category	Filgrastim, n (%)	Pegfilgrastim, n (%)	Total, n (%)
Age group (years)	0-1 month	5 (0.46)	0 (0.00)	5 (0.24)
	2 months-2 years	19 (1.74)	0 (0.00)	19 (0.91)
	3-11 years	58 (5.31)	2 (0.20)	60 (2.86)
	12-17 years	17 (1.56)	3 (0.30)	20 (0.95)
	18-64 years	403 (36.90)	370 (36.74)	773 (36.83)
	65-85 years	61 (5.59)	58 (5.76)	119 (5.67)
	>85 years	180 (16.48)	225 (22.34)	405 (19.29)
	Not specified	349 (31.96)	349 (34.66)	698 (33.25)
Sex	Male	377 (34.52)	312 (30.98)	689 (32.83)
	Female	436 (39.93)	577 (57.30)	1,013 (48.26)

	Unknown / Not specified	279 (25.55)	118 (11.72)	397 (18.91)
Case seriousness	Serious	1,069 (97.89)	947 (94.04)	2,016 (96.05)
	Non-serious	23 (2.11)	60 (5.96)	83 (3.95)
Case priority	Expedited	241 (22.07)	853 (84.71)	1,094 (52.12)
	Non-expedited	851 (77.93)	147 (14.60)	998 (47.55)
	Direct (FDA-CTU)	0 (0.00)	7 (0.70)	7 (0.33)
Co-suspect drugs	Present	687 (62.91)	642 (63.75)	1,329 (63.32)
	Not reported	405 (37.09)	365 (36.25)	770 (36.68)
Concomitant drugs	Present	601 (55.04)	683 (67.83)	1,284 (61.17)
	Not reported	491 (44.96)	324 (32.17)	815 (38.83)
Reporter type	Health professional	974 (89.19)	831 (82.52)	1,805 (85.99)
	Consumer / non-health professional	99 (9.07)	157 (15.59)	256 (12.20)
	Unknown	19 (1.74)	19 (1.89)	38 (1.81)
Region of report	United States	271 (24.82)	366 (36.35)	637 (30.35)
	Non-United States (excluding India)	706 (64.65)	588 (58.39)	1,294 (61.65)
	India	6 (0.55)	3 (0.30)	9 (0.43)
	Unknown	109 (9.98)	50 (4.97)	159 (7.58)
Outcome	Fatal	397 (36.36)	199 (19.76)	596 (28.39)
	Other outcomes	695 (63.64)	808 (80.24)	1,503 (71.61)

Note: Percentages are calculated using drug-specific denominators (filgrastim n=1,092; pegfilgrastim n=1,007). Co-suspect drugs and concomitant drugs are reported as whether at least one additional drug was recorded in the ICSR (presence/absence), not as counts of drugs. Case priority is a FAERS administrative field indicating submission classification (expedited vs non-expedited; direct indicates FDA-CTU submissions)

Disproportionality signal detection (top-30 cardiac PTs)

Disproportionality analyses were conducted for the predefined PT set (top 30 cardiac PTs) within each database. Signals were classified as strong statistical signals (all criteria met), suggestive statistical signals (≥3 criteria met), or no statistical signal (<3 criteria met) according to the criteria in Table 2.

EudraVigilance

In EudraVigilance, three PT-level robust signals met all criteria (Table 5). For filgrastim biosimilars, cardiotoxicity met robust criteria (Ncomb=21, PRR=27.32, IC025=0.47, χ^2=12.68, and ROR=28.32; 95% CI 1.710-469.014) and pericarditis met strong-signal criteria (Ncomb=23, PRR=2.43, IC025=0.01, χ^2=4.14, and ROR=2.49; 95% CI 1.005-6.179). For pegfilgrastim biosimilars, cardiac disorder met strong-signal criteria (Ncomb=26, PRR=2.41, IC025=0.24, χ^2=8.88, and ROR=2.52; 95% CI 1.346-4.705).

PTs meeting suggestive statistical signal criteria in EudraVigilance included filgrastim-associated cardiac failure and pegfilgrastim-associated arrhythmia and myocardial infarction (Table 5).

Table 5 Disproportionality metrics and signal classification for selected top cardiac PTs in EudraVigilance

Drug	Preferred Term (PT)	Ncomb	PRR	IC_{025}	χ^2	ROR	95% CI (Lower–Upper)	Signal classification
Filgrastim	Cardiotoxicity	21	27.32	0.47	12.68	28.32	1.710–469.014	Strong statistical signal
Filgrastim	Pericarditis	23	2.43	0.01	4.14	2.49	1.005–6.179	Strong statistical signal
Pegfilgrastim	Cardiac disorder	26	2.41	0.24	8.88	2.52	1.346–4.705	Strong statistical signal
Filgrastim	Cardiac failure	92	1.54	0.04	5.83	1.64	1.094–2.449	Suggestive statistical signal

Pegfilgrastim	Arrhythmia	31	1.95	0.14	6.85	2.04	1.185–3.516	Suggestive statistical signal
Pegfilgrastim	Myocardial infarction	41	1.70	0.10	6.20	1.79	1.126–2.837	Suggestive statistical signal

FAERS

In FAERS, twelve PT-level strong statistical signals met all criteria (Table 6): eight for filgrastim (cardiac ventricular thrombosis, pericarditis, cardiogenic shock, cardiotoxicity, tricuspid valve incompetence, myocardial ischaemia, pericardial effusion, and sinus tachycardia) and four for pegfilgrastim (left ventricular dysfunction, supraventricular tachycardia, cardiac disorder, and ventricular tachycardia).

Beyond strong statistical signals, two PTs met suggestive statistical signal criteria signal criteria for filgrastim (cardiac arrest and cardiac failure) and four PTs met suggestive statistical signal criteria for pegfilgrastim (arrhythmia, cardiac failure congestive, palpitations, and myocardial infarction), consistent with the prespecified tiering approach (Table 7) (Fig.3).

Table 6 FAERS disproportionality metrics and signal classification for selected top cardiac PTs

Drug	Preferred Term (PT)	Ncomb	PRR	IC_{025}	χ^2	ROR	95% CI (Lower–Upper)	Signal classification
Filgrastim	Cardiac ventricular thrombosis	55	94.34	0.78	47.07	99.34	6.128–1610.428	Strong statistical signal
Filgrastim	Pericarditis	52	7.37	0.55	30.47	7.68	3.285–17.971	Strong statistical signal
Filgrastim	Cardiogenic shock	15	6.37	0.27	8.06	6.45	1.471–28.272	Strong statistical signal
Filgrastim	Cardiotoxicity	46	5.58	0.48	23.48	5.79	2.600–12.879	Strong statistical signal
Filgrastim	Tricuspid valve incompetence	21	4.46	0.27	9.14	4.53	1.549–13.243	Strong statistical signal
Filgrastim	Myocardial ischaemia	18	3.06	0.10	5.49	3.09	1.144–8.366	Strong statistical signal
Filgrastim	Pericardial effusion	57	3.03	0.32	17.60	3.14	1.790–5.505	Strong statistical signal
Filgrastim	Sinus tachycardia	39	2.37	0.16	8.36	2.42	1.305–4.482	Strong statistical signal
Pegfilgrastim	Left ventricular dysfunction	39	4.90	0.49	21.12	5.06	2.353–10.886	Strong statistical signal
Pegfilgrastim	Supraventricular tachycardia	27	2.26	0.11	5.97	2.30	1.158–4.562	Strong statistical signal
Pegfilgrastim	Cardiac disorder	69	2.10	0.23	13.61	2.18	1.429–3.339	Strong statistical signal
Pegfilgrastim	Ventricular tachycardia	39	2.06	0.13	7.22	2.11	1.209–3.673	Strong statistical signal
Filgrastim	Cardiac arrest	84	1.88	0.16	11.44	1.95	1.317–2.893	Suggestive statistical signal
Filgrastim	Cardiac failure	187	1.54	0.13	14.81	1.66	1.278–2.143	Suggestive statistical signal
Pegfilgrastim	Arrhythmia	128	1.87	0.23	19.97	1.99	1.466–2.708	Suggestive statistical signal
Pegfilgrastim	Cardiac failure congestive	44	1.64	0.02	4.32	1.67	1.025–2.716	Suggestive statistical signal

Pegfilgrastim	Palpitations	99	1.44	0.05	6.04	1.49	1.083–2.055	Suggestive statistical signal
Pegfilgrastim	Myocardial infarction	89	1.38	0.01	4.20	1.41	1.014–1.972	Suggestive statistical signal

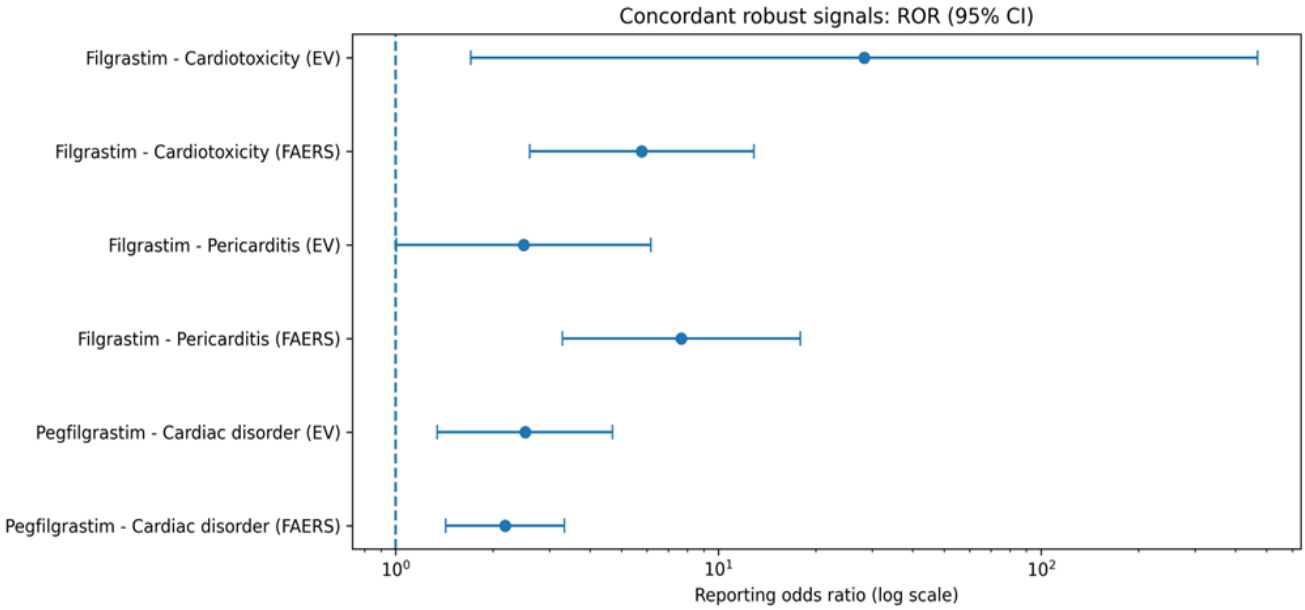

Fig. 3 Concordant strong statistical signals across databases: reporting odds ratio (ROR) with 95% confidence interval (log scale). EV denotes EudraVigilance.

Table 7 Cross-database comparison of robust cardiac safety signals

Drug	Preferred Term (PT)	EudraVigilance	FAERS	Cross-database interpretation
Filgrastim	Cardiotoxicity	Strong statistical signal	Strong statistical signal	Concordant strong statistical signal
Filgrastim	Pericarditis	Strong statistical signal	Strong statistical signal	Concordant strong statistical signal
Pegfilgrastim	Cardiac disorder	Strong statistical signal	Strong statistical signal	Concordant strong statistical signal
Filgrastim	Cardiac ventricular thrombosis	No statistical signal (evaluated)	Strong statistical signal	Strong statistical signal in FAERS; no statistical signal in EudraVigilance under top-30 framework
Filgrastim	Cardiogenic shock	No statistical signal (evaluated)	Strong statistical signal	Strong statistical signal in FAERS; no statistical signal in EudraVigilance under top-30 framework
Filgrastim	Myocardial ischaemia	No statistical signal (evaluated)	Strong statistical signal	Strong statistical signal in FAERS; no statistical signal in EudraVigilance under top-30 framework
Filgrastim	Pericardial effusion	No statistical signal (evaluated)	Strong statistical signal	Strong statistical signal in FAERS; no statistical signal in EudraVigilance under top-30 framework

Filgrastim	Sinus tachycardia	No statistical signal (evaluated)	Strong statistical signal	Strong statistical signal in FAERS; no statistical signal in EudraVigilance under top-30 framework
Filgrastim	Tricuspid valve incompetence	No statistical signal (evaluated)	Strong statistical signal	Strong statistical signal in FAERS; no statistical signal in EudraVigilance under top-30 framework
Pegfilgrastim	Left ventricular dysfunction	No statistical signal (evaluated)	Strong statistical signal	Strong statistical signal in FAERS; no statistical signal in EudraVigilance under top-30 framework
Pegfilgrastim	Supraventricular tachycardia	No statistical signal (evaluated)	Strong statistical signal	Strong statistical signal in FAERS; no statistical signal in EudraVigilance under top-30 framework
Pegfilgrastim	Ventricular tachycardia	No statistical signal (evaluated)	Strong statistical signal	Strong statistical signal in FAERS; no statistical signal in EudraVigilance under top-30 framework

**Because the PT set was selected as the top 30 PTs within each database, cross-database comparisons should consider that a PT may fall outside the other database's prespecified PT set. In this study, the PTs that were strong statistical signals in FAERS but not in EudraVigilance were included in the EudraVigilance top-30 PT set but did not meet strong-signal criteria in EudraVigilance.*

DISCUSSION

This dual-database disproportionality study assessed cardiac adverse-event reporting patterns for filgrastim and pegfilgrastim biosimilars in EudraVigilance and FAERS. Three concordant strong statistical signals were identified across both databases: cardiotoxicity and pericarditis for filgrastim and cardiac disorder for pegfilgrastim. FAERS additionally identified additional strong statistical signals within this design. These findings should be interpreted strictly as hypothesis-generating evidence derived from spontaneous reporting systems and not as estimates of incidence or proof of causality, consistent with established pharmacovigilance guidance [7,8].

A key contribution of this work is the structured comparison of signal strength across two major pharmacovigilance systems. Cross-database concordance can support prioritization by reducing the likelihood that a signal is driven solely by a single database's reporting structure, submission pathways, or coding conventions. However, concordance should not be interpreted as confirmation because spontaneous reporting sources can share correlated biases and both databases lack exposure denominators and validated outcome adjudication.

The concordant filgrastim-pericarditis signal is clinically meaningful because it highlights an inflammatory pericardial phenotype that may prompt acute evaluation in medically complex populations with multiple competing etiologies. Although temporality and causality cannot be assessed here, the appearance of an inflammatory cardiovascular phenotype is compatible with broader observations that G-CSF exposure has been linked to inflammatory vascular reactions such as aortitis [14,17], supporting biological plausibility for inflammation-mediated cardiovascular presentations in susceptible patients.

The concordant filgrastim-cardiotoxicity signal requires cautious interpretation because "cardiotoxicity" can function as an attribution term in oncology reporting rather than a clinically adjudicated diagnosis. Accordingly, this signal should be treated as a prioritization finding and refined through downstream analyses (e.g., evaluation of co-reported cardiac PT clusters, concomitant therapies, and clinically anchored endpoints) and validated in longitudinal healthcare data.

The concordant pegfilgrastim-cardiac disorder signal also requires cautious interpretation because "cardiac disorder" is a broad MedDRA PT that can be used when diagnostic specificity is limited at the time of reporting. A statistically strong association for a broad PT may reflect a true underlying clinical pattern, but it may also reflect coding and documentation practices rather than a single well-defined diagnosis. Signals involving broad or non-specific PTs should therefore be treated as screening findings and refined through downstream approaches such as PT clustering and validation using clinically anchored endpoints in structured healthcare datasets.

Differences between FAERS and EudraVigilance in signal emergence can reflect variation in report composition, diagnostic intensity, coding specificity, and attribution practices. Although top-30 selection can introduce non-overlap across databases, in this study the additional FAERS-strong PTs were also within the EudraVigilance top-30 PT set but did not meet strong statistical criteria

there, suggesting differences in relative reporting strength and/or reporting practices rather than selection artifacts alone.

A consistent descriptive observation across both databases was the higher proportion of fatal outcomes reported in filgrastim-associated cardiac reports compared with pegfilgrastim-associated reports. This pattern must be interpreted conservatively because fatality fields in spontaneous reporting systems are not adjudicated endpoints and may be influenced by confounding by indication, disease severity, comorbidity burden, and concomitant chemotherapy. Accordingly, these proportions should not be interpreted as comparative mortality risk but can inform hypothesis prioritization for validation in data sources that support confounder adjustment.

Methodological considerations are important for correct interpretation. First, disproportionality analyses were constructed as a within-class comparison within the extracted cardiac SOC dataset (union of reports containing filgrastim and/or pegfilgrastim). This approach supports comparative reporting assessment between the two agents but does not estimate risk relative to the entire database background and may not detect class effects shared by both products. Second, restricting analyses to the top-30 PTs improves stability and interpretability but may miss rarer cardiac events outside the selected PT list.

This study's strengths include the use of two major pharmacovigilance systems, conservative multi-metric signal criteria, and explicit documentation of FAERS overlap handling. Limitations are those inherent to spontaneous reporting systems, including under-reporting, missingness, stimulated reporting, confounding by indication, and limited clinical granularity (dose, duration, time-to-onset, comorbidities, and concomitant therapies). In addition, biosimilar product identification in spontaneous reports may be incomplete or inconsistent; therefore, inference at the individual biosimilar product level is constrained when brand-level identifiers are missing or ambiguously recorded.

Overall, the concordant strong statistical signals identified here (filgrastim-pericarditis, filgrastim-cardiotoxicity, and pegfilgrastim-cardiac disorder) should be prioritized for follow-up evaluation using pharmacoepidemiologic designs in longitudinal healthcare data (claims/EHR) with appropriate comparator groups, confounder control, and time-to-onset assessment, consistent with pharmacovigilance planning principles [22].

CONCLUSION

This dual-database pharmacovigilance analysis provides a focused assessment of cardiac adverse-event reporting associated with filgrastim and pegfilgrastim biosimilars using EudraVigilance and FAERS. Three cardiac signals—cardiotoxicity and pericarditis for filgrastim and cardiac disorder for pegfilgrastim—were consistently identified as concordant strong statistical signals across both databases, supporting their prioritization for further evaluation.

Additional FAERS strong statistical signals were observed, including pericardial effusion, sinus tachycardia, myocardial ischaemia, tricuspid valve incompetence, cardiogenic shock, cardiac ventricular thrombosis, left ventricular dysfunction, supraventricular tachycardia, and ventricular tachycardia, underscoring differences in reporting patterns and coding practices between pharmacovigilance systems. These findings should be interpreted within the recognized limitations of spontaneous reporting data. Disproportionality analyses identify patterns of reporting that are useful for hypothesis generation and signal prioritization, but they do not provide incidence estimates or establish causality.

Overall, integrating conservative signal criteria with cross-database evaluation supports targeted cardiac safety surveillance of G-CSF biosimilars. The concordant signals identified here represent high-priority candidates for validation using pharmacoepidemiologic designs in longitudinal healthcare datasets, where exposure denominators, temporal relationships, and confounding factors can be more rigorously addressed.

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