Research Article

Signal Mining and Analysis of Drug-Induced Myelosuppression: A Real-World Study From FAERS

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Abstract

Introduction: Drug-induced myelosuppression (DIM) is a serious side effect of several medications, particularly chemotherapy, immunosuppressants, and targeted therapies, which can lead to infections, anemia, and bleeding. While these drugs are effective, their adverse effects can disrupt treatment plans and reduce quality of life. However, early identification of DIM remains challenging, as many associated drugs do not explicitly list this risk, complicating clinical monitoring.

Methods: This study utilized the FDA Adverse Event Reporting System (FAERS) database to perform signal mining and assess the risks of DIM. Reports from the first quarter of 2004 to the third quarter of 2024 were analyzed using signal detection algorithms such as Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Empirical Bayesian Geometric Mean (EBGM). These methods helped identify drug signals related to DIM and explore risk factors and occurrence patterns.

Results: The study analyzed 21 380 adverse event reports related to DIM, showing a significant increase in the number of reports since 2019, peaking at 3501 in 2021. Among patients, 50.2% were female, 35.5% were male, and the majority (44.42%) were aged between 18 and 65. Breast cancer patients had the highest DIM incidence (10.6%). Geographically, China reported the most cases (57.4%), followed by Japan (12.4%), and the United States (6.76%). The drugs most frequently linked to DIM included trastuzumab, bevacizumab, venetoclax, methotrexate, and pertuzumab. Additionally, 12 new drug signals were identified that were not labeled for DIM risk, including PERTUZUMAB, SODIUM CHLORIDE, and MESNA, which showed particularly strong or unexpected associations.

Conclusion: This study identifies new DIM-related drug signals and emphasizes the need for early detection to improve clinical management and optimize treatment regimens. The findings provide valuable evidence for drug safety monitoring and can help reduce DIM-related risks in cancer treatment.

Plain Language Summary

Drug-induced myelosuppression (DIM) is a condition where certain medications cause a decrease in blood cells, which can lead to serious health problems like infections, anemia, and bleeding. This is especially a concern for cancer patients who are treated

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with chemotherapy, targeted therapies, and immunotherapy. However, it is often difficult to predict which drugs might cause this side effect, especially once the drugs are already on the market. In this study, we used real-world data from the FDA's Adverse Event Reporting System (FAERS) to find out which drugs are most likely to cause DIM. By analyzing over 21,000 reports from patients between 2004 and 2024, we identified several drugs that are strongly linked to DIM, including some that hadn't been officially labeled for this risk. Our findings help improve the understanding of DIM, allowing doctors to better monitor patients and reduce the chances of severe complications. This research provides important information that can help doctors choose safer treatment options for cancer patients, and it can also guide regulatory agencies in improving drug safety warnings.

Keywords
drug-induced myelosuppression (DIM), FAERS database, adverse event reporting, signal mining, reporting odds ratio (ROR), drug safety, risk assessment, personalized treatment regimens

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Introduction

Drug-induced myelosuppression (DIM) is a common and serious adverse reaction in drug therapy, involving the suppression of hematopoietic function in the blood system, leading to reductions in white blood cells, red blood cells, and platelets. In severe cases, it can result in complications such as infections, anemia, and bleeding.[1] Myelosuppression is a known side effect of many drugs, particularly chemotherapeutic agents, immunosuppressants, and certain targeted therapies. The clinical manifestations of DIM are often subtle, typically emerging in the later stages of treatment, posing significant challenges to patients' health and treatment outcomes.[2] With the increasing variety of medications and the continuous development of therapeutic methods, DIM has garnered growing attention in both clinical practice and drug regulation.

Statistically, DIM is especially common in cancer treatment, with several chemotherapeutic agents such as cyclophosphamide and paclitaxel shown to induce myelosuppression by directly affecting hematopoietic cells in the bone marrow.[3,4] Additionally, some targeted therapies and immunotherapies, including certain BCL-2 inhibitors like Venetoclax and immune checkpoint inhibitors, have also been associated with myelosuppression-related adverse reactions in clinical applications.[5,6] While these drugs offer significant therapeutic benefits for major diseases like cancer, their adverse effects can impact patients' treatment plans and quality of life, potentially leading to treatment interruption or even death.

Risk assessment and early identification of drug-induced myelosuppression are crucial for clinical treatment. However, due to the diversity and complexity of adverse reactions, many potential DIM risks remain underrecognized, especially during long-term post-market drug use. Therefore, post-market safety monitoring and pharmacovigilance have become critical tools for identifying and managing these risks. The FDA Adverse Event Reporting System (FAERS) provides a valuable database that records global drug adverse event reports, including those related to DIM.[7] This study leverages the FAERS database to conduct signal mining and thoroughly analyze the potential risks of drug-induced myelosuppression. We will apply common signal detection algorithms, such as the Disproportionality Analysis (DPA) and Bayesian models, to identify drug signals associated with myelosuppression and further explore its occurrence patterns and risk factors. Through this research, we aim to provide scientific evidence on drug safety for regulatory agencies, clinicians, and patients, enhancing drug safety monitoring and promoting the optimization of personalized treatment regimens to reduce the risk of DIM.

Materials and Methods

Data Source and Process

Adverse event data for this study were obtained from the FDA Adverse Event Reporting System (FAERS) database (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html). This database has been publicly available since 2004, and the data for this study were downloaded from the FAERS database covering adverse event reports from the first quarter of 2004 to the third quarter of 2024. This study used publicly available data from the FDA Adverse Event Reporting System (FAERS) and did not involve human participants, human tissue, or identifiable private information. Therefore, ethical approval and informed consent were not required, in accordance with institutional and international guidelines.

For data with the same "caseid" (report code) from the FAERS database, only the most recent report based on the date was retained, and duplicate reports were removed. Drug names were standardized according to the RxNorm drug normalization nomenclature to ensure consistency across the FAERS data. The International Medical Terminology Dictionary, version 27.1 (MedDRA 27.1), was used to match the primary term (PT) for "MYELOSUPPRESSION" adverse events.

Table 1. Two-By-Two Contingency Table for Disproportionality Analysis of DIM-Related Adverse Events.

	DIM-Related adverse events	Other adverse events	Total
Suspected drug	a	b	a + b
Other drugs	c	d	c + d
Total	a + c	b + d	a + b + c+d

Abbreviation: a, number of reports containing both the target drug and target adverse drug reaction; b, number of reports containing other adverse drug reaction of the target drug; c, number of reports containing the target adverse drug reaction of other drugs; d, number of reports containing other drugs and other adverse drug reactions.

After standardizing drug and adverse event names, reports of myelosuppression and the primary suspected (PS) drugs were collected. These reports were characterized by gender, age, weight, indication, reporting country, and outcome. This study complies with the RECORD guidelines.[8]

Signal Analysis Algorithms

In this study, disproportionality analysis (DPA), a commonly used algorithm in pharmacovigilance research, was employed to detect potential signals of drug-related myelosuppression adverse events. The disproportionality analysis is a widely used data mining technique that compares the observed frequency ratios between exposed and unexposed populations using a 2 × 2 contingency table to analyze the association between drugs and adverse events (Table 1).

For this study, the following signal detection algorithms were used to calculate signal strength: Reporting Odds Ratio (ROR),[9] Proportional Reporting Ratio (PRR),[10] Bayesian Confidence Propagation Neural Network (BCPNN),[11] and Empirical Bayesian Geometric Mean (EBGM).[12] Adverse event signals were considered valid if they met the positive signal criteria for these four algorithms (Table 2). After examining adverse events not mentioned in the FDA drug labeling (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm), valid signals were classified as new adverse event signals.

All data in this study were processed and statistically analyzed using R version 4.4.0 and MS Excel. The data extraction and analysis workflow is shown in Figure 1.

Results

Basic Characteristics of Adverse Events Related to Myelosuppression

As of the third quarter of 2024, the FAERS database contained a total of 21 380 adverse event reports related to myelosuppression. The number of reports related to myelosuppression was relatively low before 2010, but has shown a continuous and accelerating upward trend since then, particularly after 2015. In 2021, the number of reports peaked at 3501 cases (Figure 2). To further explore the trend, a polynomial fitting curve was plotted, showing a rapid upward trajectory. The coefficient of determination (R^2 = 0.938) indicates that the model explains 93.80% of the data variability, suggesting that the trend has high reference value. This sustained increase may be attributed to multiple factors, including the expanded clinical application of new myelosuppressive agents (e.g., targeted therapies and immunotherapies), increased global use of cancer treatments, and the gradual improvement of pharmacovigilance systems, especially in countries such as China where spontaneous reporting has become more standardized in recent years.

Table 2. Four Major Algorithms Used for Signal Detection.

Algorithms	Equation	Criteria
ROR	ROR = ad/b/c 95%CI = $e^{\ln(ROR)\pm1.96(1/a+1/b+1/c+1/d)^{\wedge}0.5}$	Lower limit of 95% CI > 1, N ≥3
PRR	PRR = a(c + d)/c/(a + b) χ^2 = [(ad-bc)^2](a + b + c+d)/[(a + b)(c + d)(a + c)(b + d)]	PRR ≥2, χ^2 ≥ 4, N ≥3
BCPNN	IC = $\log_2$a(a + b + c+d)(a + c)(a + b) 95%CI = E(IC) ± 2V(IC)^0.5	IC025>0
EBGM	EBGM = a(a + b + c+d)/(a + c)/(a + b) 95%CI = $e^{\ln(EBGM)\pm1.96(1/a+1/b+1/c+1/d)^{\wedge}0.5}$	EBGM05>2

Abbreviation: a, number of reports containing both the target drug and target adverse drug reaction; b, number of reports containing other adverse drug reaction of the target drug; c, number of reports containing the target adverse drug reaction of other drugs; d, number of reports containing other drugs and other adverse drug reactions. 95%CI, 95% confidence interval; N, the number of reports; χ2, chi-squared; IC, information component; IC025, the lower limit of 95% CI of the IC; E(IC), the IC expectations; V(IC), the variance of IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95% CI of EBGM.

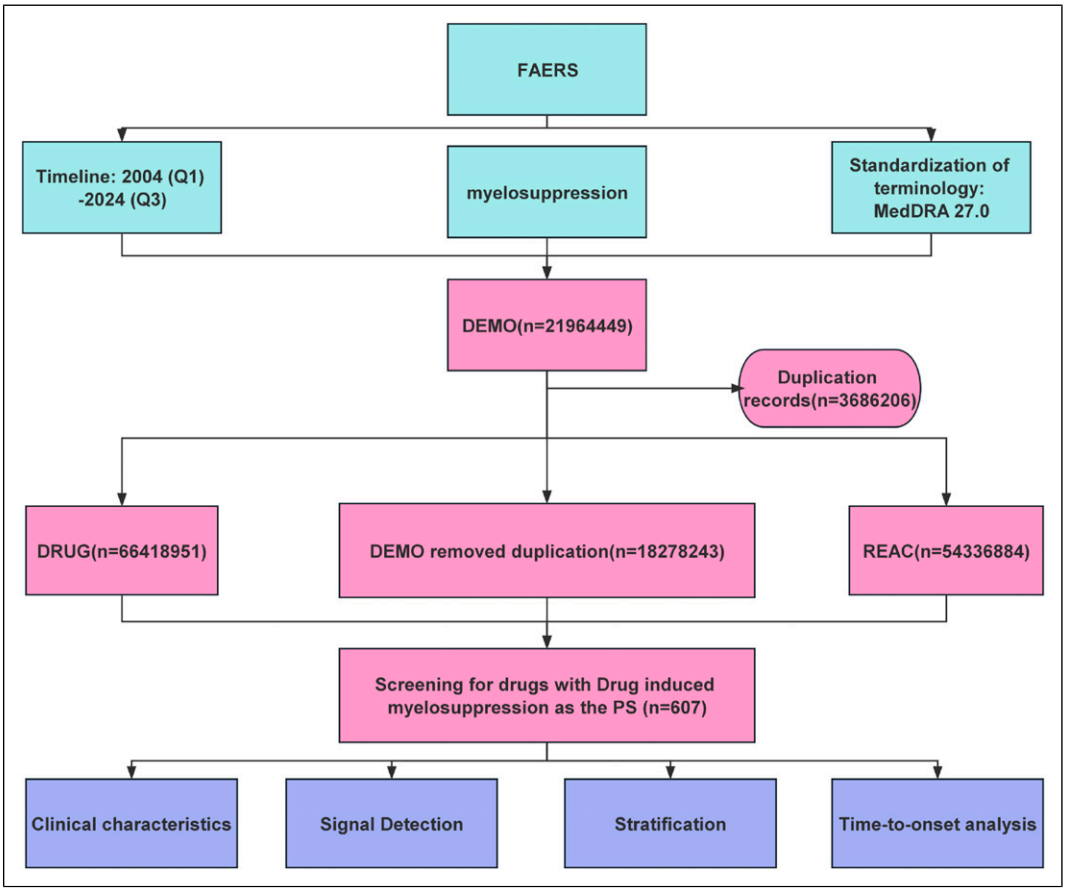

Figure 1. Analysis Process of Drug-Induced Bone Marrow Suppression Signals.

Table 3 presents the demographic characteristics of the population associated with myelosuppression adverse events. Of the reports, 50.2% were from female patients, 35.5% from male patients, and 14.3% had an unknown gender. The age distribution revealed that the largest proportion of adverse events occurred in patients aged 18-65 years (44.42%) among those with known age information. The highest proportion of myelosuppression adverse events was observed in patients weighing 50-70 kg (26.07%), although 56.33% of the reports did not provide weight information. Notably, the highest incidence of myelosuppression was observed in patients with breast cancer (10.6%), followed by acute myeloid leukemia (5.2%) and cases with an unknown indication (3.7%). Geographically, the highest number of reports were from China (57.40%), followed by Japan (12.40%) and the United States (6.76%).

Drug Analysis

The top 30 drugs associated with the highest number of drug-induced myelosuppression adverse events are shown in Figure 3. The top five drugs were TRASTUZUMAB (1130 reports), BEVACIZUMAB (1062 reports), VENETOCLAX (982 reports), METHOTREXATE (803 reports), and PERTUZUMAB (709 reports). Among these, BEVACIZUMAB and PERTUZUMAB were noted as not explicitly mentioning the risk of drug-induced myelosuppression in their prescribing information. Of the top 30 drugs with the highest number of myelosuppression-related adverse events, five drugs did not include the risk of myelosuppression in their labels.

Signal Detection of Drug-Induced Myelosuppression Adverse Events

The statistical results of disproportionality analysis revealed that among the top 30 drugs with the highest signal strength for adverse events, 12 drugs had not mentioned the risk of drug-induced myelosuppression in their labels, indicating a new adverse event signal. The top five drugs with the highest signal strength were TISLELIZUMAB [n = 596, ROR = 694.31 (623.06-773.72)], TORIPALIMAB [n = 192, ROR = 664.4 (550.13-802.41)], GLUCOSE* [n = 48, ROR = 215.08 (156.69-295.23)], CERALASERTIB [n = 1, ROR = 170.79 (19.95-1462)], and DEXKETOPROFEN* [n = 1, ROR = 106.75 (13.35-853.53)].

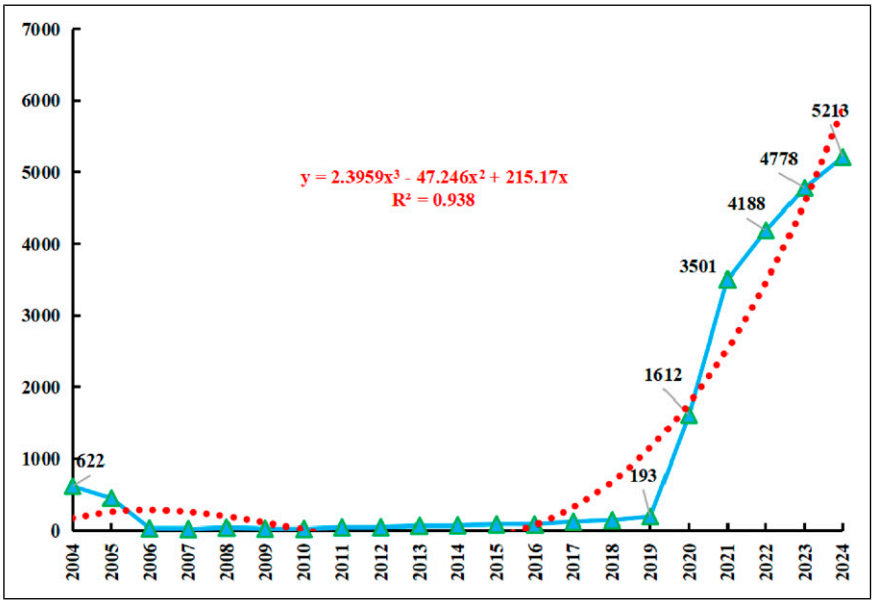

Figure 2. Reporting Trends of Adverse Events in Drug Induced Bone Marrow Inhibition.

The five drugs with the highest number of reports, which did not mention the adverse event in their labels, were PERTUZUMAB* [n = 709, ROR = 96.41 (89.11-104.3)], SODIUM CHLORIDE* [n = 668, ROR = 87.73 (80.93-95.1)], MESNA* [n = 56, ROR = 77.33 (58.81-101.68)], FRUQUINTINIB* [n = 49, ROR = 49.98 (37.46-66.69)], and GLUCOSE* [n = 48, ROR = 215.08 (156.69-295.23)].

A total of 10 drugs, including TRASTUZUMAB, PERTUZUMAB, SODIUM CHLORIDE, CYTARABINE, TISLELIZUMAB, ERIBULIN, OBINUTUZUMAB, GILTERITINIB, EPIRUBICIN, and TORIPALIMAB, reported more than 100 myelosuppression-related adverse events (Table 4). Notably, PERTUZUMAB* and SODIUM CHLORIDE* were not mentioned in the prescribing information as being associated with myelosuppression-related adverse events.

Figure 4 displays a Venn diagram of four algorithms—ROR, PRR, MGPS, and BCPNN—where 129 drugs met the positive signal criteria for all four algorithms. To further investigate more rigorous adverse event signals, we plotted a forest plot (Figure 5) for the drugs that met the positive criteria for all four algorithms and had the top 30 signal strengths. Among these, TRASTUZUMAB, VENETOCLAX, PERTUZUMAB*, CYCLOPHOSPHAMIDE, CYTARABINE, TISLELIZUMAB, ERIBULIN, DARATUMUMAB, OBINUTUZUMAB, GILTERITINIB, ABEMACICLIB, EPIRUBICIN, TORIPALIMAB, BRENTUXIMAB VEDOTIN, and TRASTUZUMAB EMTANSINE each had more than 100 myelosuppression-related adverse events. GLUCOSE*, TRILACICLIB*, PERTUZUMAB*, MESNA*, FRUQUINTINIB*, NIZATIDINE*, and NECITUMUMAB* were identified as having no explicit mention of drug-induced myelosuppression in their prescribing information.

Induction Time Analysis

The analysis of the induction time for adverse drug reactions is crucial for drug safety monitoring, clinical medication guidance, regulatory decision-making, and drug development improvement. In this study, the median induction time for adverse events related to PALBOCICLIB was the shortest at 180 days. The Weibull distribution shape parameter (β) was found to be < 1, with a 95% confidence interval (CI) also <1, indicating that the adverse event rate is considered to decrease over time (early failure-type curve). Among the drugs analyzed, TRASTUZUMAB, BEVACIZUMAB*, VENETOCLAX, METHOTREXATE, and PERTUZUMAB* were identified as having myelosuppression induction times following the early failure-type curve, as shown in Table 5.

Discussion

The occurrence of drug-induced myelosuppression involves multiple factors, primarily including the type of drug, its mechanism of action, as well as the individual characteristics and health status of the patient.[13] In recent years, with the increasing frequency of drug usage, drug-induced myelosuppression has gradually attracted widespread clinical attention. Chemotherapy drugs, targeted therapies, and other medications can directly or indirectly affect hematopoietic function in the bone marrow, inhibiting the proliferation and differentiation of hematopoietic stem cells, leading to reductions in white blood cells, red blood cells,

Table 3. Baseline Characteristics of Drug-Induced Bone Marrow Suppression Population.

Characteristics	Case numbers	Case proportion (%)
Number of events	21 380	-
Gender		
Female	10 725	50.2%
Male	7594	35.5%
Miss	3061	14.3%
Age		
Median (IQR)	57	
<18	1511	7.07%
18-65	9497	44.42%
65-85	4954	23.17%
>85	215	1.01%
Miss	5203	24.34%
Weight(KG)		
<50	2077	9.71%
50-70	5574	26.07%
70-90	1447	6.77%
≥90	238	1.11%
Miss	12 044	56.33%
Top 5 indication		
Breast cancer	2271	10.6%
Acute myeloid leukaemia	1102	5.2%
Product used for unknown indication	781	3.7%
Medication dilution	728	3.4%
Plasma cell myeloma	670	3.1%
Top 5 Reported countries		
China	12 272	57.40%
Japan	2652	12.40%
United STATES	1445	6.76%
Germany	750	3.51%
Canada	444	2.08%

Abbreviation: interquartile range, IQR.

and platelets, thereby triggering myelosuppression. Chemotherapy agents such as cyclophosphamide, cytarabine, and anthracyclines (e.g., doxorubicin) have potent cytotoxic effects, directly acting on hematopoietic cells in the bone marrow to suppress their normal function, resulting in extensive myelosuppression.[14,15] Additionally, targeted therapies like BCL-2 inhibitors (e.g., venetoclax) and FLT3 inhibitors (e.g., gilteritinib) indirectly impact hematopoiesis in the bone marrow by inhibiting the growth and survival of cancer cells, leading to adverse effects.[16] Immunotherapy agents such as PD-1 inhibitors (e.g., toripalimab) and anti-CD20 monoclonal antibodies (e.g., obinutuzumab) activate the immune system and may induce immune-mediated myelosuppression.[17]

Susceptible Populations and Clinical Management

According to data from the FAERS database up to the third quarter of 2024, a total of 21 380 adverse event reports related to myelosuppression were recorded. Notably, since 2019, the number of such reports has significantly increased, reaching 3501 reports in 2021, indicating a rapid upward trend in the occurrence of myelosuppression. The polynomial fitting model ($R^2 = 0.938$) indicates a strong upward trend in DIM-related reports over time. However, this trend may not solely reflect an increase in true drug-induced myelosuppression risk. It is also likely influenced by improved pharmacovigilance infrastructure, increased clinician awareness, and heightened reporting activity, especially in recent years with the expansion of post-marketing surveillance systems.

In this study, women and patients aged 18-65 years showed a higher frequency of reported drug-induced myelosuppression. Although causality cannot be established from FAERS data, these findings suggest that additional clinical attention may be needed for these subgroups. Clinicians may consider closer monitoring, including more frequent blood tests and early evaluation of hematologic parameters. Pretreatment risk assessments could also help identify susceptible individuals. While dose adjustment based on age or sex requires further prospective validation, our results highlight the

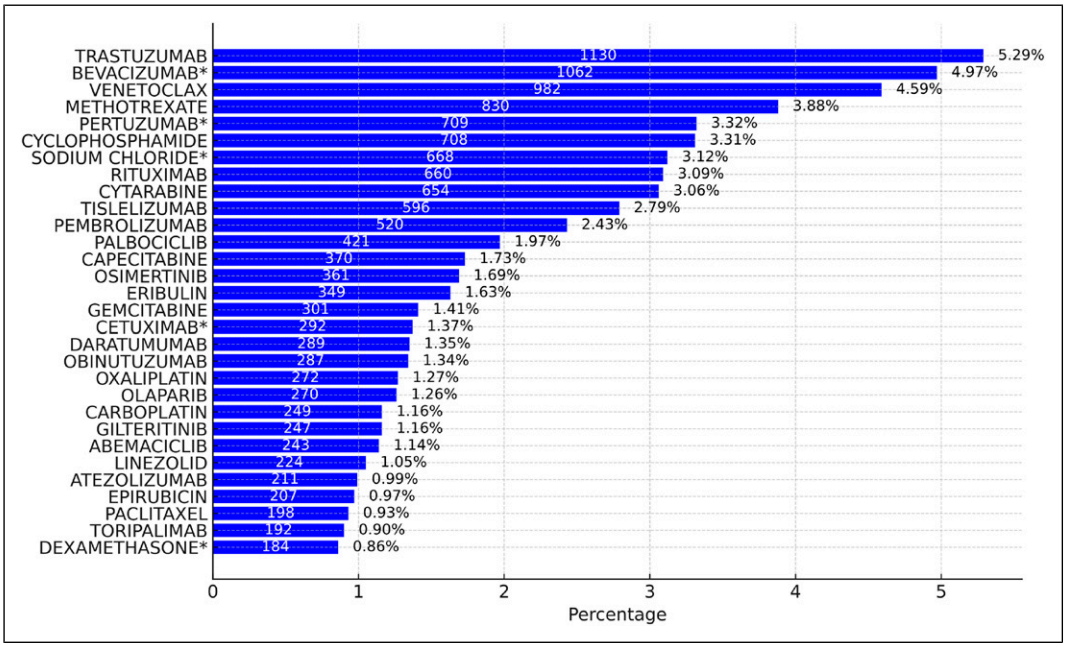

Figure 3. The Top 30 Drugs Reported for Drug-Induced Bone Marrow Suppression.
Note: * Indicates New Signals Not Mentioned in the Manual.

need for individualized pharmacovigilance strategies to enhance treatment safety in high-risk populations.

Additionally, the influence of weight on myelosuppression adverse events was significant, with the highest proportion of patients falling within the 50-70 kg weight range (26.07%). However, 56.33% of patients did not provide weight information. This data suggests that although heavier patients may face a higher risk of adverse drug reactions, missing weight data remains a potential issue. Regarding the distribution of adverse events by indication, breast cancer (10.6%) had the highest incidence of myelosuppression, followed by acute myeloid leukemia (5.2%). Furthermore, some adverse events were reported in patients with unspecified indications (3.7%), suggesting that some patients might be at risk of myelosuppression due to unclear drug mechanisms or improper treatment choices. Geographically, the majority of DIM reports originated from China (57.4%), followed by Japan (12.4%) and the United States (6.76%). These disparities likely reflect differences in pharmacovigilance systems, reporting practices, and regulatory emphasis rather than true incidence rates. For example, China's recent advancements in post-marketing surveillance may have contributed to the surge in adverse event reporting. Likewise, the U.S. FDA's open-access FAERS system facilitates active reporting by healthcare providers and patients. In contrast, regions with limited pharmacovigilance infrastructure or underdeveloped reporting systems may be underrepresented. Additionally, variations in drug usage patterns and patient demographics across countries could further influence the observed distribution. These geographical imbalances introduce potential reporting bias, which may affect the interpretation and generalizability of the findings. Therefore, caution is warranted when extrapolating these results to countries with different healthcare systems or lower reporting capacity.

Based on these analyses, clinical practices should develop personalized medication monitoring plans tailored to the characteristics of different patient populations. For female patients and those aged 18-65, closer monitoring of drug use is essential, especially for drugs with a high risk of myelosuppression (e.g., certain chemotherapy agents).[18] For patients with low body weight or missing weight data, special attention should be given to potential differences in drug metabolism, with regular assessments of blood routine tests to detect potential myelosuppression risks early.[19] Additionally, for patients with breast cancer or acute myeloid leukemia, given the high incidence of myelosuppression in these populations, bone marrow function monitoring should be strengthened during treatment to ensure early detection of abnormalities and timely adjustment of treatment plans. Finally, for patients from different countries or regions, geographical differences in drug safety should be considered, and treatment strategies and monitoring measures should be appropriately adjusted to ensure patient safety and therapeutic efficacy.

Major High-Risk Drug Categories

Based on FAERS data and the ROR algorithm, this study identified 15 high-risk drug signals associated with myelosuppression, mainly involving chemotherapy, targeted therapy, and immunotherapy agents. While a higher ROR suggests a stronger statistical association, it does not imply clinical

Table 4. Top 30 Drugs in Signal Strength Ranking.

Drug name	Case reports	ROR (95%CI)	PRR (95%CI)	EBGM(EBGM05)	IC(IC025)
TISLELIZUMAB	596	694.31 (623.06-773.72)	388.23 (224037.9)	377.43 (344.74)	8.56 (8.42)
TORIPALIMAB	192	664.4 (550.13-802.41)	375.57 (71166.02)	372.21 (317.84)	8.54 (8.29)
GLUCOSE*	48	215.08 (156.69-295.23)	172.08 (8155.52)	171.7 (131.73)	7.42 (6.97)
CERALASERTIB	1	170.79 (19.95-1462)	142.49 (140.66)	142.49 (23.63)	7.15 (4.84)
DEXKETOPROFEN*	1	106.75 (13.35-853.53)	95 (93.11)	94.99 (16.68)	6.57 (4.33)
TRILACICLIB*	18	101.88 (62.48-166.12)	91.13 (1605.11)	91.06 (60.48)	6.51 (5.81)
PERTUZUMAB*	709	96.41 (89.11-104.3)	87.02 (58353.03)	84.16 (78.8)	6.4 (6.28)
GILTERITINIB	247	93.99 (82.37-107.25)	84.86 (20257.7)	83.9 (75.12)	6.39 (6.2)
DEXRAZOXANE	33	89.6 (62.58-128.27)	81.19 (2612.83)	81.07 (60.04)	6.34 (5.82)
SODIUM CHLORIDE*	668	87.73 (80.93-95.1)	79.88 (50465.02)	77.41 (72.36)	6.27 (6.16)
ERIBULIN	349	86.35 (77.29-96.47)	78.62 (26340.65)	77.36 (70.51)	6.27 (6.11)
MESNA*	56	77.33 (58.81-101.68)	71.01 (3859.48)	70.82 (56.32)	6.15 (5.75)
AMPIROXICAM*	1	56.93 (7.52-431.02)	53.44 (51.51)	53.43 (9.82)	5.74 (3.58)
BEPRIDIL	1	53.37 (7.08-402.49)	50.29 (48.37)	50.29 (9.27)	5.65 (3.5)
CYTARABINE	654	52.05 (48.05-56.39)	49.2 (29973.27)	47.73 (44.63)	5.58 (5.46)
FRUQUINTINIB*	49	49.98 (37.46-66.69)	47.28 (2217.3)	47.17 (37.06)	5.56 (5.14)
ZANUBRUTINIB	66	40.38 (31.53-51.7)	38.61 (2413.01)	38.49 (31.3)	5.27 (4.91)
OBINUTUZUMAB	287	38.84 (34.48-43.75)	37.21 (9989.35)	36.73 (33.24)	5.2 (5.02)
PIPOBROMAN*	2	32.85 (8-134.86)	31.67 (59.46)	31.66 (9.71)	4.98 (3.27)
TRASTUZUMAB	1130	32.04 (30.15-34.05)	30.97 (31079.76)	29.39 (27.93)	4.88 (4.79)
LORACARBEF*	1	30.5 (4.15-224.17)	29.48 (27.55)	29.48 (5.55)	4.88 (2.77)
ENFORTUMAB VEDOTIN	93	29.03 (23.6-35.71)	28.11 (2424.13)	28 (23.54)	4.81 (4.5)
POLATUZUMAB VEDOTIN	71	28.89 (22.8-36.62)	27.98 (1843.47)	27.89 (22.88)	4.8 (4.46)
EPIRUBICIN	207	28.63 (24.91-32.9)	27.74 (5289.87)	27.48 (24.46)	4.78 (4.58)
ALANINE*	1	28.47 (3.88-208.75)	27.58 (25.64)	27.58 (5.21)	4.79 (2.68)
IOBENGUANE (131 I)	2	26.69 (6.53-109.04)	25.91 (47.95)	25.91 (7.98)	4.7 (2.99)
IDARUBICIN	34	26.6 (18.91-37.44)	25.83 (811.24)	25.79 (19.38)	4.69 (4.19)
IFOSFAMIDE	85	25.06 (20.19-31.11)	24.38 (1900.48)	24.29 (20.27)	4.6 (4.29)
CHLOROTHIAZIDE*	1	24.4 (3.34-178.11)	23.75 (21.82)	23.75 (4.5)	4.57 (2.47)
DECITABINE	69	23.69 (18.64-30.1)	23.08 (1454.38)	23.01 (18.83)	4.52 (4.17)

Note: * indicates new signals not mentioned in the manual.

severity or causality. Currently, no standardized threshold defines a "high-risk" drug based solely on disproportionality metrics, which serve primarily for signal detection. However, drugs showing strong, consistent signals—particularly those without prior labeling for myelosuppression—warrant further validation. If confirmed by real-world studies or clinical trials, these findings could inform regulatory actions such as label revisions, enhanced surveillance, or clinical warnings.

Chemotherapy Drugs (e.g., Cyclophosphamide, Cytarabine, Epirubicin, Eribulin): Chemotherapy drugs primarily induce myelosuppression by directly killing rapidly dividing cells, including hematopoietic stem cells in the bone marrow. Cyclophosphamide, an alkylating agent widely used for the treatment of various cancers, cross-links with DNA to inhibit DNA replication and repair, leading to a reduction in bone marrow hematopoietic function and subsequently causing myelosuppression.[20] Cytarabine, an antimetabolite, inhibits DNA synthesis, directly affecting cell proliferation in the bone marrow, resulting in a reduction of white blood cells, red blood cells, and platelets.[21] Similarly, Epirubicin, an anthracycline anticancer agent, binds to DNA and inhibits its synthesis, leading to widespread myelosuppression.[22] Eribulin, a microtubule inhibitor, prevents tumor cell division and, while mainly targeting cancer cells, also exerts toxic effects on hematopoietic cells in the bone marrow.[23] These drugs require close monitoring of blood routine tests in clinical practice, with timely adjustments to drug doses to prevent severe myelosuppression.

Targeted Therapy Drugs: Targeted therapy drugs act through specific molecular targets and indirectly affect hematopoietic function, leading to myelosuppression. Several drugs identified in this study have well-documented mechanisms contributing to myelosuppression, which align with existing literature. Venetoclax, a BCL-2 inhibitor, induces apoptosis in cancer cells but also disrupts normal hematopoiesis by inhibiting BCL-2 in bone marrow cells, leading to cytopenias.[24] Gilteritinib, used for FLT3-mutated AML, suppresses leukemic proliferation but can also impair normal bone marrow cell growth, increasing the risk of myelosuppression.[25] Abemaciclib, a CDK4/6 inhibitor, inhibits cancer

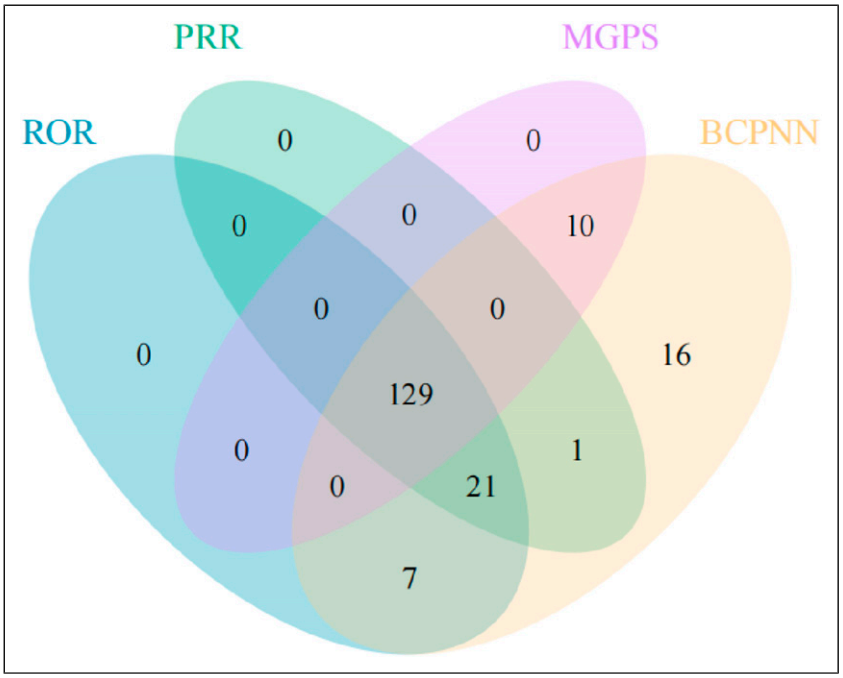

Figure 4. Venn Diagrams of Drugs Under Four Algorithms: ROR, PRR, MGPS, and BCPNN.

cell cycle progression but concurrently reduces white blood cell and platelet counts by affecting hematopoietic progenitor cells.[26] Trastuzumab emtansine, an antibody-drug conjugate targeting HER2-positive cells, delivers cytotoxic agents that may inadvertently damage bone marrow function, resulting in hematologic toxicity.[27]

These findings are consistent with prior pharmacological and clinical reports, supporting the robustness of our signal detection results. However, the identification of additional signals in less-studied drugs—such as pertuzumab*, sodium chloride*, and mesna*—extends the current understanding of drug-induced myelosuppression and highlights areas where further clinical validation is needed.

Immunotherapy Drugs: Immunotherapy drugs exert anticancer effects by modulating the immune system but may sometimes induce immune-mediated myelosuppression or suppress normal hematopoiesis through immune responses. Tislelizumab and Toripalimab, PD-1 inhibitors, enhance T-cell attacks on tumors by relieving immune checkpoint inhibition. However, this immune response may lead to immune-mediated myelosuppression.[28] Daratumumab, which targets CD38, is primarily used in the treatment of multiple myeloma. While it is effective in controlling the tumor, it can interfere with the proliferation of normal bone marrow cells, leading to myelosuppression.[29] Obinutuzumab, a CD20-targeting monoclonal antibody, is commonly used to treat B-cell-related malignancies but may affect bone marrow function by depleting B-cells, leading to myelosuppression.[30]

These drugs, through different mechanisms, directly or indirectly influence hematopoiesis in the bone marrow, resulting in a reduction in white blood cells, red blood cells, and platelets, thereby causing myelosuppression. Myelosuppressive reactions to these drugs require strict monitoring and management in clinical practice, including regular blood routine tests, adjustment of drug doses, assessment of potential side effects, and individualized treatment plans based on the patient's clinical status. By optimizing drug use strategies and enhancing drug safety monitoring, the risk of myelosuppression can be effectively reduced, improving treatment outcomes and the quality of life for patients.

Drug-Induced Onset Time and Characteristics

In this study, we analyzed the onset time of adverse events related to myelosuppression induced by drugs, and the results revealed significant differences in the onset time characteristics across various drugs. For Palbociclib, the median onset time for adverse events was 180 days. The Weibull distribution shape parameter ($\beta < 1$, 95% CI < 1) indicates that the incidence of myelosuppression-related adverse events is relatively high in the early stages of treatment and decreases over time, exhibiting a typical "early failure-type curve." Similar onset time characteristics were observed for Trastuzumab, Bevacizumab, Venetoclax, Methotrexate, and Pertuzumab, which may cause rapid and significant disruption to the immune system or hematopoietic function during the initial phase of treatment, resulting in a higher incidence of adverse events in the short term.[31]

The early failure-type curves observed in this study indicate that the risk of myelosuppression is elevated during the initial phase of treatment, particularly within the first

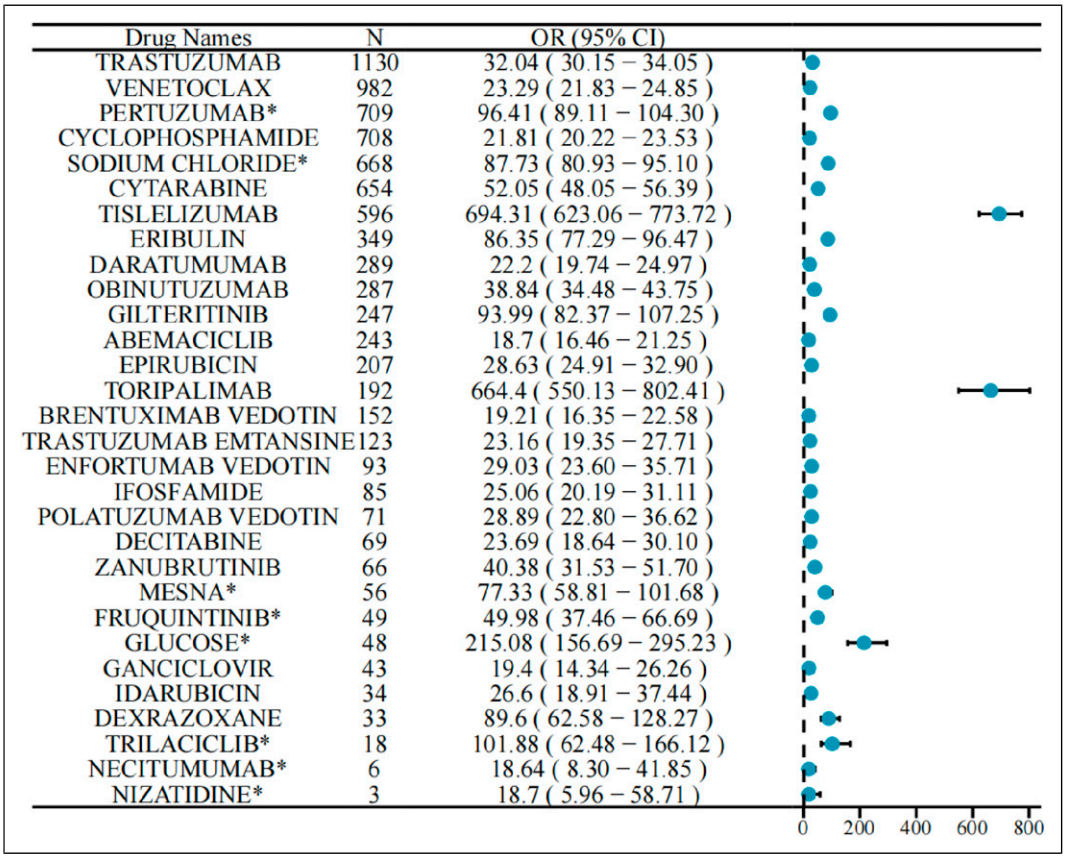

Figure 5. Forest Map of Positive Drugs With the Top 20 Signal Strengths Under the ROR Algorithm.
Note: * Indicates New Signals Not Mentioned in the Manual.

2-4 weeks. This highlights the importance of early monitoring in clinical practice. Frequent blood tests—including white blood cell, red blood cell, and platelet counts—should be performed to promptly detect hematologic toxicity. For high-risk patients, such as those receiving combination therapies or with pre-existing blood disorders, individualized dose adjustments or delayed dose escalation may be warranted. These strategies can facilitate timely intervention and reduce the risk of severe complications.

Limitations

Despite rigorous signal detection, our study has several limitations. While duplicate reports were removed using unique case

Table 5. Analysis of the Occurrence Time and Weibull Distribution of Drug-Induced Bone Marrow Suppression Adverse Events.

	Date of onset (days)		Weibull distribution		
PT	Case reports	Median(d)(IQR)	Scale parameter: α(95%CI)	Shape parameter: β(95%CI)	Type
TRASTUZUMAB	1130	1038	14.44 (13.08~15.80)	0.73 (0.70~0.75)	Early failure
BEVACIZUMAB*	1062	630	17.80 (15.54~20.05)	0.72 (0.68~0.76)	Early failure
VENETOCLAX	982	3064.5	33.53 (28.61~38.44)	0.63 (0.60~0.66)	Early failure
METHOTREXATE	830	4352.5	45.10 (30.81~59.39)	0.41 (0.38~0.45)	Early failure
PERTUZUMAB*	709	180	12.89 (11.79~14.00)	0.99 (0.94~1.04)	Early failure
CYCLOPHOSPHAMIDE	708	1278.5	13.05 (11.40~14.71)	0.71 (0.67~0.74)	Early failure
RITUXIMAB	668	3657.5	12.20 (10.89~13.52)	0.73 (0.70~0.76)	Early failure
CYTARABINE	660	467.5	28.88 (23.08~34.68)	0.63 (0.58~0.67)	Early failure
TISLELIZUMAB	654	155.5	12.29 (11.07~13.51)	0.90 (0.85~0.94)	Early failure
PEMBROLIZUMAB	596	326.5	15.11 (13.53~16.70)	0.83 (0.79~0.88)	Early failure

Note: * indicates new signals not mentioned in the manual; CI, Confidence interval; IQR, Interquartile range.

identifiers, undetected duplicates may still exist. Geographic reporting bias may also influence results, as countries with more active pharmacovigilance systems (e.g., China, Japan) contributed disproportionately to the total reports. Additionally, drug-specific treatment durations were not uniformly available, limiting our ability to assess the time-dependent nature of myelosuppression risk. Finally, although 12 new signals were identified, these findings have not yet been validated in other databases or clinical settings. Further studies using real-world clinical data or prospective cohorts are warranted to confirm these associations and establish causal relationships.

Conclusion

This study conducted an in-depth analysis of drug-induced myelosuppression (DIM) using the FDA Adverse Event Reporting System (FAERS) and identified drug signals associated with DIM, exploring its occurrence characteristics and risk factors. Through the analysis of 21 380 DIM-related adverse event reports, the study revealed that female patients, individuals aged 18 to 65, and breast cancer patients are at higher risk for DIM. Additionally, factors such as weight and geographic distribution were found to influence the occurrence of DIM. The study identified drugs such as trastuzumab, bevacizumab, and venetoclax as being more strongly associated with DIM, with some of these drugs not clearly indicating the risk of myelosuppression in their labeling, and new risk signals were discovered.

Furthermore, through signal mining methods, 12 new drug signals were identified, showing a high signal strength but not labeled with the DIM risk. This research provides critical drug safety data for regulatory agencies, clinicians, and patients, advancing the scientific basis for DIM risk assessment and early detection. By optimizing drug usage monitoring and individualizing treatment plans, the risk of DIM could be reduced, improving treatment outcomes and quality of life for patients. However, the findings still require confirmation through further clinical validation and long-term data analysis.

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Ethical Statement

This study used publicly available data from the FDA Adverse Event Reporting System (FAERS) and did not involve human participants, human tissue, or identifiable private information. Therefore, ethical approval and informed consent were not required, in accordance with institutional and international guidelines.

Author contributions

Kaiyue Xia : Methodology, Data curation, Conceptualization. **ShuPeng Chen** : Writing – original draft. **Yingjian Zeng** : Methodology, Data curation, Conceptualization. **Nana Tang:** Methodology, Formal analysis, Data curation. **Meiling Zhang :** Writing – review & editing. All authors contributed to manuscript revision, and read and approved the submitted version.

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Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data Availability Statement

The original contributions presented in the study are included in the article/Supplemental Material, further inquiries can be directed to the corresponding author.

Supplemental Material

Supplemental material for this article is available online.

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