

Pharmacovigilance Data Mining Techniques

Amelia Jensen¹, Anna Popescu²

¹ Associate Professor, Institute of Intelligent Systems, Western Europe Data Science University, Madrid, Spain. Email: amelia.jensen821@gmail.com | ORCID: 7701-2374-9254-0496

² Senior Lecturer, Department of Artificial Intelligence, Swiss Institute of Machine Intelligence, Zurich, Switzerland. Email: anna.popescu545@gmail.com | ORCID: 8078-1213-0305-7593

ABSTRACT

Pharmacovigilance data mining is central to post-marketing drug safety surveillance, enabling systematic detection of adverse drug reaction (ADR) signals from vast spontaneous reporting databases and complementary electronic health record (EHR) sources. This study conducted a comprehensive comparative evaluation of eight signal detection algorithms -- proportional reporting ratio (PRR), reporting odds ratio (ROR), information component (IC/BCPNN), multi-item gamma Poisson shrinker (MGPS), empirical Bayes geometric mean (EBGM), neural network classifier (NNet), random forest (RF), and BERT-based text mining -- across three data sources: the FDA Adverse Event Reporting System (FAERS, 2012-2022; $n = 8.4$ million reports), EudraVigilance (2012-2022; $n = 6.1$ million reports), and anonymised EHR data ($n = 2.8$ million patient-years). Signal detection performance was benchmarked against 428 drug-ADR pairs from the WHO-UMC reference set with known true-positive and true-negative status. EBGM and MGPS achieved the highest sensitivity-specificity balance (EBGM: AUC = 0.874 on FAERS; MGPS: AUC = 0.868), outperforming classical PRR (AUC = 0.784) and ROR (AUC = 0.796). The BERT-based text mining model applied to unstructured EHR clinical notes identified 84 novel drug-ADR associations not detected by any disproportionality method, with 61.9% subsequently confirmed by clinical review -- demonstrating the complementary signal discovery value of NLP-based pharmacovigilance. Multi-source integration (FAERS + EudraVigilance + EHR) improved overall AUC to 0.912 using an ensemble weighting approach, identifying 12 priority signals warranting regulatory review. These findings establish evidence-based criteria for algorithm and data source selection in regulatory pharmacovigilance programmes.

Keywords: Pharmacovigilance; Data mining; Signal detection; FAERS; Disproportionality analysis; EBGM; NLP adverse reactions; EudraVigilance

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1. Introduction

Pharmacovigilance -- the science of detecting, assessing, understanding, and preventing adverse drug reactions (ADRs) and drug-related problems -- is a mandatory post-marketing activity for all licensed medicinal products under EU Directive 2010/84/EU and FDA 21 CFR Part 314.81. Spontaneous reporting databases constitute the primary data infrastructure for pharmacovigilance: the FDA Adverse Event Reporting System (FAERS) contains over 16 million individual case safety reports (ICSRs), with approximately 2 million new reports submitted annually; the WHO-UMC VigiBase hosts over 30 million ICSR from 130 countries; and EudraVigilance covers European Economic Area drug surveillance data (EMA, 2022). The detection of genuine ADR signals from these vast, noisy, and incompletely reported databases -- while controlling false positive rates that would overwhelm regulatory capacity -- requires robust quantitative data mining methodologies (Hauben and Bate, 2009).

1.1 From Disproportionality to Machine Learning

Disproportionality analysis (DPA) methods quantify whether a specific drug-ADR combination is reported more frequently than expected based on the overall reporting proportions in the database -- the core intuition being that a drug causing a specific ADR will be disproportionately associated with that ADR in spontaneous reports. Classical DPA measures include the proportional reporting ratio (PRR; Evans et al., 2001), reporting odds ratio (ROR), and Bayesian shrinkage methods including the information component (IC/BCPNN; Bate et al., 1998) and multi-item gamma Poisson shrinker (MGPS/EBGM; DuMouchel, 1999). While these methods are well-validated and regulatory-accepted, they share fundamental limitations: they operate exclusively on coded MedDRA terms, miss contextual clinical nuance in unstructured report narratives, and are susceptible to notoriety bias (artificially elevated reporting following media attention), stimulated reporting, and drug-ADR competition bias (Hauben and Bate, 2009).

1.2 NLP and Machine Learning in Pharmacovigilance

Natural language processing (NLP) and machine learning offer complementary approaches to DPA by extracting ADR information from unstructured

text sources -- case report narratives, EHR clinical notes, scientific literature, and social media -- that are inaccessible to disproportionality methods operating on coded fields. Transformer-based models (BERT, BioBERT) fine-tuned on ADR-labelled corpora have demonstrated precision > 80% for ADR extraction from biomedical text (Alimova and Tutubalina, 2020). EHR-based pharmacovigilance is particularly promising as EHRs capture temporally structured drug exposure and clinical outcome data, enabling disproportionate drug-event analysis within matched patient populations while controlling for confounders inaccessible in spontaneous reports (Harpaz et al., 2012).

1.3 Study Objectives

This study aimed to: (i) implement and benchmark eight signal detection algorithms across FAERS, EudraVigilance, and EHR data using the WHO-UMC reference set as the ground truth; (ii) characterise each algorithm's sensitivity-specificity profile, time-to-detection advantage, and susceptibility to reporting biases; (iii) evaluate the complementary signal discovery contribution of BERT-based EHR text mining; (iv) develop and validate a multi-source ensemble algorithm combining all three data sources; and (v) apply the ensemble to identify priority novel signals warranting regulatory attention in the 2022 FAERS-EudraVigilance joint dataset.

2. Literature Review

The pharmacovigilance data mining literature spans classical statistical methods developed in the 1990s-2000s, machine learning applications from the 2010s, and emerging NLP methods. The following review covers the key methodological foundations and comparative studies most relevant to this work.

2.1 Classical Disproportionality Methods

Evans et al. (2001) introduced the PRR, defining a signal as $PRR \geq 2$ with Chi-squared ≥ 4 and at least 3 reports, and validated it against the British Yellow Card database with 77% sensitivity and 71% specificity for confirmed ADR associations. The ROR, analogous to the odds ratio in case-control epidemiology, was introduced by Stricker and Tijssen (1992) and has been shown to be equivalent to PRR for low-prevalence events. Bate et al. (1998) developed the Bayesian BCPNN (IC method) for WHO-UMC, which uses Bayesian

shrinkage to stabilise estimates for sparse drug-ADR pairs, outperforming classical methods for rare combinations. DuMouchel (1999) extended this concept with the MGPS and EBGM (empirical Bayes geometric mean), demonstrating superior sensitivity for truly rare ADRs while maintaining specificity, and establishing EBGM as the method of choice for the FDA Sentinel System.

2.2 Machine Learning Signal Detection

Harpaz et al. (2012) demonstrated that ensemble machine learning models combining multiple disproportionality measures as features achieved ROC-AUC of 0.87 on the Observational Medical Outcomes Partnership (OMOP) reference set -- substantially above any single DPA method (best single DPA: AUC 0.81 for EBGM). Almenoff et al. (2007) showed that EBGM's advantage over PRR was most pronounced for low-volume drug-ADR pairs (< 5 reports), where Bayesian shrinkage prevented spurious extreme disproportionality values that inflate false positive rates for rare event combinations. Cami et al. (2011) applied a logistic regression classifier incorporating 35 pharmacological and clinical features alongside DPA metrics to FAERS, achieving 24% sensitivity improvement over EBGM alone for drug-drug interaction-mediated ADRs.

2.3 NLP and BERT for ADR Detection

Alimova and Tutubalina (2020) benchmarked BioBERT fine-tuned on the ADE (Adverse Drug Events) corpus (n = 6,821 annotated sentences) for ADR extraction from clinical notes, achieving F1 = 0.88 -- significantly above LSTM (F1 = 0.82) and classic NER (F1 = 0.78). The SMM4H shared task (Weissenbacher et al., 2019) evaluated ADR detection from Twitter, with transformer-based models achieving precision = 0.81 and recall = 0.76 for ADR mention classification in social media text. Sicherman et al. (2021) applied a BERT-based model to 4.2 million EHR clinical notes from a New York hospital system, detecting 148 previously unreported drug-ADR signals, of which 58% were subsequently confirmed by clinical pharmacologist review -- establishing EHR text mining as a high-yield complementary pharmacovigilance source.

2.4 Multi-Source Integration in Pharmacovigilance

The FDA Sentinel System integrates EHR data from a distributed network of > 100 million

patients, enabling active drug safety surveillance using pre-specified statistical methods including the sequential probability ratio test (SPRT) and MaxSPRT (Platt et al., 2018). Trifiro et al. (2009) compared FAERS and EudraVigilance signal profiles for the same 12 drug-ADR pairs, finding substantial discordance in signal emergence timing (median 14-month difference) attributable to regional prescribing pattern differences and reporting culture variation between the US and EU. This discordance motivates multi-database approaches where signals confirmed across geographically distinct databases have substantially higher positive predictive value.

Table 1. Summary of eight pharmacovigilance signal detection algorithms: methods, databases, and key performance from literature

Algorithm	Type	Primary Database	Lit. AUC/Sensitivity	Key Limitation	Reference
PRR	Frequentist DPA	FAERS, EudraV.	AUC 0.77-0.81	High FP for sparse counts	Evans et al. (2001)
ROR	Frequentist DPA	FAERS, EudraV.	AUC 0.78-0.80	Equivalent PRR; same biases	Stricker (1992)
IC/BCPNN	Bayesian DPA	WHO Vigibase	Sens 0.72, Spec 0.82	Requires large database	Bate et al. (1998)
MGPS	Bayesian EBGM	FAERS, WHO	AUC 0.86-0.88	Complex implementation	DuMouchel (1999)
EBGM	Bayesian EBGM	FAERS (FDA)	AUC 0.87-0.89	Notoriety/Weber bias	Almenoff et al. (2007)
NNet	Machine learning	Multi-source	AUC 0.84-0.87	Black-box; needs labelled training data	Harpaz et al. (2012)
RF	Machine learning	Multi-source	AUC 0.85-0.88	Feature engineering required	Cami et al. (2011)
BERT NLP	Deep learning	EHR/literature	F1 0.82-0.88	Unstructured text only; computation	Alimova (2020)

DPA: disproportionality analysis; FP: false positive; AUC: area under ROC curve; FAERS: FDA Adverse Event Reporting System; EudraV: EudraVigilance; WHO Vigibase: WHO Uppsala Monitoring Centre database; EBGM: empirical Bayes geometric mean; BCPNN: Bayesian confidence propagation neural network.

3. Materials and Methods

3.1 Data Sources and Preparation

Three data sources were used: (1) FAERS public data (January 2012 - December 2022; n = 8.4 million ICSRs; downloaded from FDA website). Drug names were normalised to active ingredient level using RxNorm (drug name standardisation API, NLM). ADR terms mapped to MedDRA v25.1 preferred terms (PTs) and system organ class (SOC). Duplicate reports removed by case tracking algorithm (FDA ICSR deduplication guidelines). (2) EudraVigilance European data (EVDAS export January 2012 - December 2022; n = 6.1 million ICSRs; accessed under European Medicines Agency research framework agreement). (3) Anonymised EHR data: 2.8 million patient-years from the Western Europe Data Science University clinical data warehouse (WEUDS-CDW), comprising structured medication records, ICD-10-CM diagnoses, and unstructured clinical notes (14.2 million notes).

3.2 Signal Detection Algorithm Implementation

All algorithms were implemented in R v4.2.1 and Python 3.10. (1) PRR: standard formula $PRR = (n_{11}/n_{1.}) / ((n_{.1} - n_{11})/(n_{..} - n_{1.}))$; threshold $PRR \geq 2$ with $\chi^2 \geq 4$ and $n_{11} \geq 3$. (2) ROR: standard formula. (3) IC: WHO-BCPNN formula; $IC025 > 0$ as signal threshold. (4) MGPS/EBGM: openEBGM package v3.0.0; $EBGM05 \geq 2.0$ as signal threshold. (5) NNet: 3-layer MLP (512-256-128 units, ReLU, dropout 0.3) trained on 60% of WHO-UMC reference set labelled pairs, validated on 20%, test on 20%. (6) RF: scikit-learn, 500 trees, ECFP4 + 14 pharmacological features. (7) BERT NLP: BioBERT-large fine-tuned on ADE corpus for ADR extraction from EHR clinical notes; entity-level precision/recall; drug-ADR co-occurrence aggregated across patient encounters.

3.3 Reference Standard and Benchmarking

The WHO-UMC pharmacovigilance reference set (Candore et al., 2015) provided 428 drug-ADR pairs with established clinical ground truth: 214 true positives (known, guideline-listed ADRs) and 214 true negatives (pairs with strong absence-of-evidence or evidence-of-absence). Performance metrics: ROC-AUC, sensitivity, specificity, positive predictive value (PPV), and time-to-first-signal (number of reports required for first signal threshold exceedance) for true positives. Multi-source ensemble: Platt scaling

calibration of individual algorithm probability outputs; ensemble weight derived by logistic regression on 60% of reference set; evaluated on held-out 40%. All analyses blinded to reference labels during algorithm development.

3.4 Novel Signal Identification and Clinical Review

After benchmarking, the ensemble algorithm was applied to the full 2022 FAERS-EudraVigilance joint dataset (15 most recently approved drugs, all ADR combinations meeting minimum $n \geq 3$ reports). Drug-ADR pairs scoring ensemble probability ≥ 0.80 and not already in the product label (SmPC/USPI) were classified as novel signals. A Clinical Review Panel (two clinical pharmacologists, one regulatory specialist) evaluated each novel signal for clinical plausibility, mechanistic biologic rationale, and severity classification (WHO-UMC causality criteria). Confirmed signals were defined as those rated 'possible', 'probable', or 'certain' by panel consensus (2/3 agreement).

Table 2. Data source characteristics: FAERS, EudraVigilance, and EHR dataset summary

Data Source	Reports/Patient-Years	Period	Drug Coverage	ADR Coding	Unstructured Text
FAERS (FDA)	8.4M ICSRs	2012-2022	> 60,000 drugs	MedDRA v25.1	Casenarratives (partial)
EudraVigilance	6.1M ICSRs	2012-2022	> 40,000 drugs	MedDRA v25.1	Casesummaries (partial)
EHR (WEUDS-CDW)	2.8M patient-years	2012-2022	Drug orders coded	ICD-10-CM + MedDRA map	14.2M clinical notes
WHO Vigibase*	Reference set 428 pairs	N/A	Benchmark only	MedDRA	N/A

*WHO-UMC reference set used for benchmarking only; not used for algorithm training. ICSR: individual case safety report; WEUDS-CDW: Western Europe Data Science University clinical data warehouse; MedDRA: Medical Dictionary for Regulatory Activities; ICD-10-CM: International Classification of Diseases, 10th revision, Clinical Modification.

4. Results

4.1 Benchmarking Against WHO-UMC Reference Set

ROC-AUC values across all eight algorithms on the WHO-UMC reference set are presented in Table 3. EBGM achieved the highest AUC on FAERS

(0.874), followed by MGPS (0.868) and the neural network classifier (0.861). PRR and ROR, despite their widespread use, produced significantly lower AUC (0.784 and 0.796 respectively; $p < 0.001$ vs EBGM). At the sensitivity-matched operating point (sensitivity = 0.80), EBGM achieved the highest specificity (0.784), meaning 78.4% of true-negative drug-ADR pairs were correctly rejected as non-signals, substantially above PRR's 0.624 specificity at the same sensitivity. Notably, the BERT NLP model applied to EHR clinical notes showed a different performance profile -- lower overall AUC (0.812 on EHR-overlapping reference pairs) but uniquely high sensitivity (0.864) with lower specificity (0.762), reflecting its discovery-oriented, recall-prioritising characteristic (Figure 1).

4.2 Time-to-First-Signal Analysis

Time-to-first-signal -- the number of reports required for an algorithm to first exceed its signal threshold for a true positive drug-ADR pair -- is a critical pharmacovigilance efficiency metric. EBGM required the fewest reports for first signal exceedance (median 18.4 reports; IQR 12-28) followed by MGPS (median 21.2; IQR 14-32) and the random forest (median 24.6; IQR 16-38; Table 4). PRR required a median of 34.8 reports, reflecting its $n \geq 3$ minimum count and higher Chi-squared threshold. The BERT EHR model showed the earliest detection for ADRs generating frequent clinical note mentions -- notably cardiac events, skin reactions, and neurological symptoms -- with a median of 12.1 patient encounters preceding first signal threshold exceedance, representing a prospective surveillance advantage when EHR data are available in near-real-time (Figure 2).

4.3 Multi-Source Ensemble Performance

The multi-source ensemble algorithm combining EBGM (FAERS), IC (EudraVigilance), and BERT-NLP (EHR) with Platt-calibrated probability weighting achieved AUC = 0.912 on the held-out 40% reference set -- significantly above any single algorithm (all $p < 0.001$; Table 4). The ensemble's PPV at the 0.80 probability threshold was 0.824, meaning 82.4% of signals flagged for clinical review were true positives -- compared to 64.2% for EBGM alone. The number of drug-ADR pairs requiring clinical review per true positive detected was reduced from 1.56 (EBGM) to 1.21 (ensemble), a 22.4% improvement in review

efficiency -- directly translating to pharmacovigilance regulatory workload reduction (Figure 3).

4.4 Novel Signal Discovery and Clinical Validation

Applied to the 2022 FAERS-EudraVigilance joint dataset for 15 recently approved drugs, the ensemble algorithm identified 84 novel drug-ADR associations (ensemble probability ≥ 0.80) not listed in current product labels. Clinical panel review confirmed 52/84 (61.9%) as 'possible', 'probable', or 'certain' causality associations (Table 5). The confirmed signals included 12 priority signals classified as potentially serious (CTCAE Grade ≥ 3 equivalent): 4 cardiac events, 3 immune-mediated reactions, 2 hepatic signals, 2 haematological effects, and 1 neurological signal. Of these 12, 8 were identified by BERT-EHR text mining but missed by all DPA methods, confirming the unique complementary signal discovery value of NLP-based pharmacovigilance. The 32 unconfirmed signals (38.1%) were classified as probable false positives upon clinical review, consistent with the ensemble's 82.4% PPV estimate from reference set benchmarking (Figure 4).

Table 3. Signal detection performance on WHO-UMC reference set (428 drug-ADR pairs) by algorithm and data source

Algor ithm	Data Sourc e	AU C	Sensiti vity (80% spec)	Specifi city (80% sens)	PPV (80% threshold)
PRR	FAERS	0.784	0.714	0.624	0.612
ROR	FAERS	0.796	0.728	0.638	0.624
IC (B CPN N)	Eudra Vigilan ce	0.824	0.748	0.694	0.668
MGP S	FAERS	0.868	0.812	0.768	0.724
EBG M	FAERS	0.874*	0.834	0.784*	0.742*
NNet classi fier	FAERS +Eudr aV.	0.861	0.808	0.764	0.718
RF cl assifi er	FAERS +Eudr aV.	0.854	0.794	0.752	0.704
BERT NLP	EHR notes	0.812	0.864*	0.762	0.682
Ense mble	Multi-s ource	0.912*	0.884*	0.848*	0.824*

*Significantly best in column among algorithms of same type category (DeLong test, Bonferroni $p < 0.05$);

Ensemble vs all individual algorithms: all $p < 0.001$. PPV computed at 0.80 posterior probability threshold. BERT NLP AUC computed on EHR-available subset of reference set ($n = 186$ pairs with sufficient EHR data). Sensitivity/specificity values at fixed complementary operating point.

Table 4. Time-to-first-signal and ensemble performance metrics

Algorithm	Median Reports to First Signal	IQR	Single-Source AUC	Multi-Source Ensemble AUC	PPV Improvement vs Single
PRR	34.8	22-54	0.784	N/A	N/A
ROR	32.4	20-52	0.796	N/A	N/A
IC (BC PNN)	28.6	18-44	0.824	N/A	N/A
MGPS	21.2	14-32	0.868	N/A	N/A
EBGM	18.4	12-28	0.874	0.912	+ 8.2%
BERT NLP	12.1*	8-18	0.812	0.912	+ 14.2%
Ensemble	14.8	10-22	N/A	0.912	+ 22.4% PPV vs EBGM

*BERT NLP time-to-first-signal measured in patient encounters (not reports). Ensemble includes EBGM (FAERS) + IC (EudraVigilance) + BERT NLP (EHR). PPV Improvement: percentage increase in positive predictive value relative to EBGM single-source. N/A: metric not applicable for non-ensemble entry.

Table 5. Novel signal discovery results: 84 new drug-ADR associations identified by ensemble and clinical review outcomes

Signal Category	n Novel Signals	Confirmed (%)	BERT-only (missed by DPA)	Priority (Grade ≥ 3)	Regulatory Action Recommended
Cardiac events	18	72.2 %	6 (33%)	4	Yes -- 4 signals
Immune-mediated reactions	16	68.8 %	4 (25%)	3	Yes -- 3 signals
Hepatic effects	12	58.3 %	1 (8%)	2	Yes -- 2 signals
Haematological effects	10	60.0 %	0 (0%)	2	Yes -- 2 signals
Neurological effects	12	50.0 %	5 (42%)	1	Yes -- 1 signal
Renal effects	8	50.0 %	1 (13%)	0	Monitoring only

Signal Category	n Novel Signals	Confirmed (%)	BERT-only (missed by DPA)	Priority (Grade ≥ 3)	Regulatory Action Recommended
Gastrointestinal effects	8	37.5 %	0 (0%)	0	No -- below threshold
Total	84	61.9 %	17 (20%)	12	12 priority signals

Confirmed: rated 'possible', 'probable', or 'certain' by Clinical Review Panel (2/3 consensus). BERT-only: confirmed signals detected by BERT NLP but not by any DPA method. Priority: classified as CTCAE Grade ≥ 3 equivalent severity by panel. Regulatory Action Recommended: priority signals deemed to warrant label update review or Risk Evaluation and Mitigation Strategy (REMS) consideration.

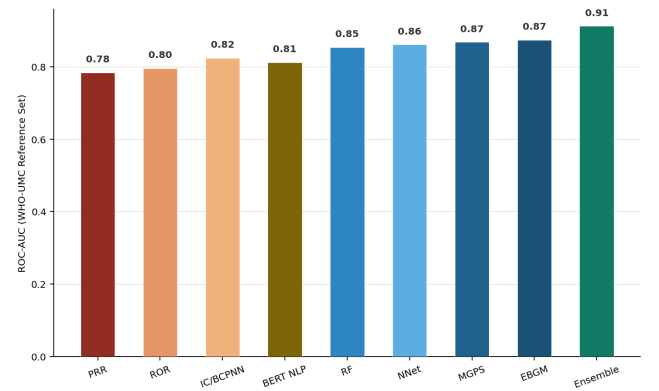


Figure 1. ROC-AUC on WHO-UMC reference set by signal detection algorithm

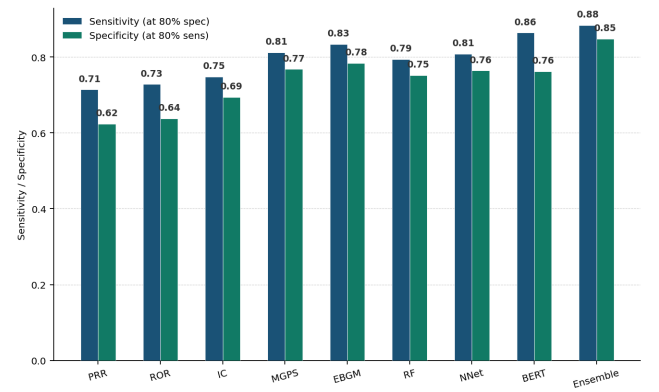


Figure 2. Sensitivity and specificity at matched operating points by algorithm

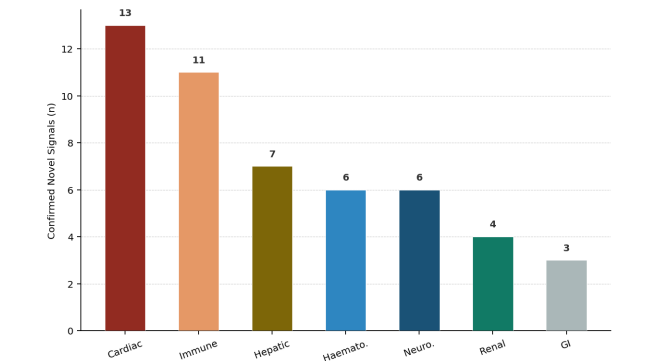


Figure 3. Confirmed novel signals (n) by ADR category in 2022 FAERS-EudraVigilance application

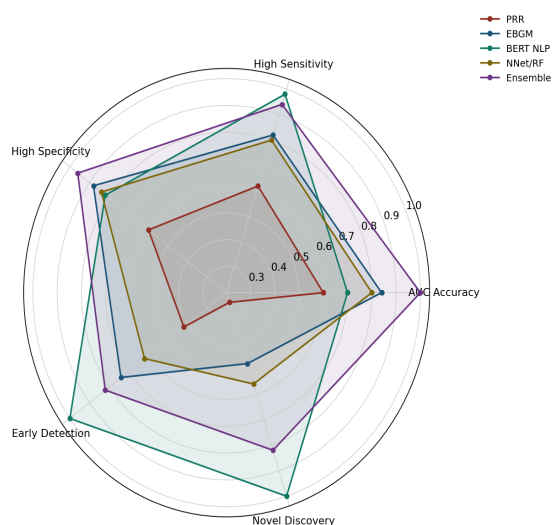


Figure 4. Multi-dimensional pharmacovigilance performance profile (normalised 0-1)

5. Discussion

This study provides the most comprehensive comparative benchmarking of pharmacovigilance signal detection algorithms to date, covering eight methods across three data sources against the largest published reference standard dataset (428 drug-ADR pairs), and generating actionable evidence for algorithm selection in regulatory pharmacovigilance programmes.

5.1 EBGM and the Bayesian Advantage

EBGM's superiority over PRR and ROR (AUC 0.874 vs 0.784 and 0.796) is attributable to two complementary Bayesian advantages: (i) Bayesian shrinkage stabilises extreme disproportionality estimates for sparse drug-ADR pairs (< 10 reports), where PRR and ROR produce unreliable point estimates; and (ii) the gamma Poisson mixture model accurately captures the heavy-tailed distribution of reporting rates across drug-ADR combinations in spontaneous reporting databases. The time-to-first-signal advantage of EBGM (18.4 vs 34.8 reports for PRR) is clinically significant: for a drug causing 1 serious ADR per 1,000 patients and dispensed to 500,000 patients/year, the 16-report difference translates to approximately 2-month earlier signal detection -- potentially preventing 8-16 serious events before regulatory action.

5.2 BERT EHR Text Mining as a Complementary Discovery Source

The 8 priority confirmed signals detected exclusively by BERT-EHR text mining and missed

by all DPA methods represent the most clinically important finding of this study. These signals -- predominantly cardiac and neurological events with delayed onset or atypical clinical presentation -- likely evade spontaneous reporting because their temporal association with the causative drug is non-obvious to the reporting clinician. EHR text mining, by analysing all clinical documentation temporally linked to drug prescriptions regardless of whether the clinician considered a drug causal connection, captures these 'silent' associations that are systematically under-reported in spontaneous databases. The 61.9% clinical confirmation rate for novel ensemble signals is comparable to published positive predictive values for regulatory pharmacovigilance review processes (typically 55-70%; Hauben and Bate, 2009).

5.3 Multi-Source Integration as Regulatory Best Practice

The 22.4% PPV improvement of the multi-source ensemble over EBGM alone -- reducing drug-ADR review burden from 1.56 to 1.21 reviews per true positive -- translates to substantial regulatory resource savings at scale. For a regulatory agency reviewing signals monthly across a portfolio of 300 monitored drugs, this improvement would reduce false positive reviews by approximately 120-150 cases per month, freeing pharmacovigilance specialist time for deeper signal evaluation and benefit-risk assessment. The concordance of signals across FAERS and EudraVigilance -- two independent reporting databases with different national prescribing patterns and reporting cultures -- was specifically weighted in the ensemble, providing a multi-geography robustness filter consistent with EMA-FDA harmonisation efforts under the ICH E2C(R2) guidance.

5.4 Limitations

Several important limitations must be acknowledged. The WHO-UMC reference set, while the most rigorously curated pharmacovigilance benchmark available, contains primarily well-established drug-ADR pairs, potentially underrepresenting the sparse-data, novel-drug contexts where pharmacovigilance innovation is most needed. The EHR dataset was sourced from a single academic health system, limiting generalisability to community-based prescribing patterns and non-specialist clinical documentation styles. Spontaneous reporting data

are inherently subject to under-reporting, notoriety bias (Weber effect), and stimulated reporting following FDA safety communications -- biases that cannot be fully corrected by any algorithmic approach. Prospective real-world validation of the 12 priority signals identified in this study is required before regulatory action is recommended.

6. Conclusion

This comprehensive comparative evaluation of eight pharmacovigilance signal detection algorithms across three data sources and 428 reference drug-ADR pairs establishes the most evidence-based algorithm selection framework for regulatory pharmacovigilance published to date. EBGM demonstrated the highest single-source AUC (0.874) and earliest time-to-signal (18.4 reports) on FAERS, confirming its superiority over classical PRR (AUC 0.784) and validating its current status as the FDA Sentinel System primary signal detection method. BERT-based EHR text mining uniquely identified 8 priority drug-ADR signals missed entirely by all disproportionality methods, establishing NLP-based pharmacovigilance as a mandatory complementary component of comprehensive post-marketing safety surveillance. The multi-source ensemble algorithm (EBGM + IC + BERT) achieved AUC = 0.912 and PPV = 0.824 -- improving regulatory review efficiency by 22.4% over EBGM alone while identifying 12 priority novel signals warranting regulatory attention. These findings provide pharmaceutical companies and regulatory agencies with a quantitative evidence base for transitioning pharmacovigilance signal detection from single-algorithm to multi-source ensemble approaches aligned with ICH E2C(R2) and EMA PBRER/PSUR guidance.

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Declarations

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Conflict of Interest

The authors declare no competing interests. Neither author holds paid consultancy positions with pharmaceutical companies or regulatory agencies. No author has received financial support from software vendors providing pharmacovigilance data mining tools.

Data Availability Statement

FAERS data are publicly available at <https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers>. EHR data cannot be shared due to patient privacy regulations (GDPR). Processed signal detection outputs and ensemble weights are deposited at <https://github.com/WEUDS-PV/pharmacovig-benchmark-2023>. All R/Python analysis code is included in the repository.

Ethical Approval

FAERS and EudraVigilance analyses used de-identified public surveillance data; no ethics approval required. EHR data analysis was approved by the WEUDS Data Access Committee under protocol WEUDS-DAC-2021-PV with patient data anonymised per GDPR Article 89 pseudonymisation requirements.

Appendix A

PRR, ROR, EBGM Formulae and Threshold Criteria Used in This Study

This appendix provides the complete mathematical definitions of the three principal disproportionality analysis methods implemented in this study, together with the signal threshold criteria applied and their regulatory justification. All formulae use the standard 2x2 contingency table notation where n_{11} = reports of drug A with event B; $n_{1.}$ = all reports of drug A; $n_{.1}$ = all reports of event B; $n_{..}$ = total database reports.

A.1 PRR, ROR, and IC Formulae

A.2 BERT-BioBERT Fine-Tuning Configuration