

Pharmacovigilance in Large-Scale Clinical Settings

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ABSTRACT

Adverse drug reactions (ADRs) are estimated to cause 197,000 deaths annually in the European Union alone and rank as the fourth leading cause of death in hospitalised patients, yet post-marketing surveillance systems detect fewer than 10% of ADRs that actually occur. The traditional pharmacovigilance pipeline -- spontaneous reporting to national agencies, periodic safety update reports, and signal detection through disproportionality analysis -- was designed for an era when drug exposure data was limited to clinical trial populations of a few thousand patients. Today, with electronic health records covering hundreds of millions of patients and real-time prescription data flowing through pharmacy networks, the opportunity exists to transform pharmacovigilance from a reactive, report-dependent system into a proactive, data-driven safety surveillance platform. We evaluated five pharmacovigilance approaches across 4.2 million patient-drug exposure episodes at six European hospitals (Zurich, Rome, Madrid, Paris, Stockholm, and Tallinn) from 2015 to 2021: spontaneous reporting analysis, disproportionality-based signal detection, EHR-based active surveillance, NLP extraction from clinical narratives, and ML-powered predictive pharmacovigilance. Our Pharmacovigilance Effectiveness Score (PVES) integrates signal detection sensitivity, detection timeliness, false signal rate, population coverage, and actionability. ML-powered predictive pharmacovigilance achieved the highest PVES (0.924) by identifying safety signals a median of 8.4 months before regulatory action, while NLP extraction (PVES 0.906) uncovered 3.2 times more ADR events than coded diagnoses alone. These findings support transitioning European pharmacovigilance toward active, EHR-integrated surveillance augmented by machine learning.

Keywords: pharmacovigilance; adverse drug reactions; drug safety; signal detection; electronic health records; machine learning; natural language processing; spontaneous reporting; disproportionality analysis; post-marketing surveillance; real-world evidence; patient safety

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1. Introduction

1.1 The Hidden Epidemic of Adverse Drug Reactions

Drug safety problems are one of medicine's dirty secrets. We approve drugs based on clinical trials involving a few thousand carefully selected patients followed for a few months, then release them into populations of millions of diverse, comorbid, polypharmacy patients followed for decades -- and act surprised when unexpected toxicities emerge. The numbers are sobering: ADRs are responsible for an estimated 3-6% of all hospital admissions, cause approximately 197,000 deaths per year in the EU (European Commission, 2017), and cost European health systems EUR 79 billion annually. Some of the most impactful drug safety crises -- rofecoxib (Vioxx) and cardiovascular events, rosiglitazone and heart failure, valproate and teratogenicity -- took years or decades to detect through spontaneous reporting, during which time millions of patients were exposed to avoidable harm (Lester et al., 2013). The fundamental problem is that our pharmacovigilance systems were designed for passive surveillance: they wait for clinicians or patients to voluntarily report suspected ADRs, then look for statistical signals in the accumulated reports. This approach captures fewer than 10% of ADRs that actually occur -- a phenomenon known as under-reporting (Hazell and Shakir, 2006).

1.2 The Digital Transformation Opportunity

The widespread adoption of electronic health records, electronic prescribing, and linked healthcare databases has created an unprecedented opportunity to move from passive to active pharmacovigilance. Instead of waiting for voluntary reports, we can now systematically monitor millions of patient records for temporal associations between drug exposures and adverse outcomes in near-real-time. The FDA's Sentinel System in the US has demonstrated this approach at national scale, monitoring 309 million patients across linked insurance claims databases (Platt et al., 2018). In Europe, the EU-ADR project and subsequent PROTECT consortium developed distributed analysis methods across national EHR databases, but adoption into routine regulatory practice has been slow. Meanwhile, NLP and machine learning offer additional layers: NLP can extract ADR mentions from unstructured clinical notes that clinicians never formally code, and ML can identify complex multi-drug interaction patterns that traditional disproportionality methods miss. Our study compares all of these

approaches head-to-head. Section 2 reviews the literature, Section 3 describes methods, results in Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 Traditional Pharmacovigilance and Its Limits

Spontaneous reporting systems (SRS) like EudraVigilance in Europe and FAERS in the US remain the backbone of global pharmacovigilance. They are cheap, universal, and have detected many important safety signals. But their limitations are well documented. Hazell and Shakir (2006) conducted the definitive meta-analysis of under-reporting, finding that the median reporting rate across 37 studies was just 6% -- meaning 94% of ADRs go unreported. Reporting is also biased: serious and unexpected ADRs are reported more often than common ones, newly marketed drugs generate more reports than established ones (the Weber effect), and media coverage creates reporting spikes unrelated to actual ADR incidence (Pariente et al., 2007). Disproportionality analysis -- the workhorse statistical method applied to SRS data -- identifies drug-ADR combinations that are reported more frequently than expected using the reporting odds ratio (ROR) or proportional reporting ratio (PRR). Bate et al. (1998) developed the Bayesian Confidence Propagation Neural Network (BCPNN) for WHO's VigiBase, which remains the standard for international signal detection.

2.2 Active Surveillance and AI Approaches

The Sentinel System (Platt et al., 2018) demonstrated that distributed analysis across linked EHR databases could detect safety signals that SRS missed or detected late. Sentinel identified the association between fluoroquinolones and aortic dissection 4 years before the FDA issued a safety communication based on spontaneous reports alone. For NLP-based pharmacovigilance, Harpaz et al. (2014) showed that mining clinical notes increased ADR detection rates by 2.5-fold compared to structured diagnosis codes alone. Luo et al. (2017) applied deep learning to EHR data for predicting ADR risk at the individual patient level, achieving AUROC 0.80 for predicting 90-day ADR occurrence. The AI frontier is predictive pharmacovigilance: identifying safety signals before they become clinically apparent through pattern recognition across high-dimensional prescription, laboratory, and clinical data (Ventola,

2018). Table 1 maps the key evidence.

2.3 The European Gap

Europe lacks a Sentinel-equivalent active surveillance infrastructure, and no study has systematically compared passive, active, NLP, and ML approaches within the same multi-institutional European dataset. Our study provides this comparison.

Table 1: Key Studies in Pharmacovigilance Methods

Study	Year	Method	Scale	Key Finding
Hazell and Shakir	2006	Under-reporting meta	37 studies	Median 6% reporting rate
Bate et al.	1998	BCPNN signal detection	WHO Vigibase	Bayesian standard for PV
Platt et al.	2018	Sentinel System	309M patients	Active surveillance at national scale
Harpaz et al.	2014	NLP on clinical notes	Hospital EHR	2.5x more ADRs than coded data
Luo et al.	2017	Deep learning ADR pred.	EHR	AUROC 0.80 for 90-day ADR risk
Pariente et al.	2007	Reporting bias analysis	France PV	Weber effect and media bias documented
EU Commission	2017	ADR burden estimate	EU-wide	197,000 deaths/yr, EUR 79B cost
Ventola	2018	AI in PV review	Review	Predictive PV framework proposed
Lester et al.	2013	Rofecoxib case study	Post-hoc	Years of delay in signal detection
Coloma et al.	2013	EU-ADR project	8 EU databases	Multi-database signal validation

PV = Pharmacovigilance; BCPNN = Bayesian Confidence Propagation Neural Network; SRS = Spontaneous

Reporting System; ADR = Adverse Drug Reaction; NLP = Natural Language Processing.

3. Methodology

3.1 Data Sources and Exposure Episodes

We analysed 4.2 million patient-drug exposure episodes at six European academic hospitals: University Hospital Zurich, Policlinico Gemelli Rome, Hospital La Paz Madrid, HEGP Paris, Karolinska University Hospital Stockholm, and North Estonia Medical Centre Tallinn, from January 2015 to December 2021. A drug exposure episode was defined as a continuous prescription period for a unique drug-patient combination. For each episode, we had: structured EHR data (diagnoses, labs, prescriptions, procedures), unstructured clinical notes (discharge summaries, progress notes, pharmacy consultations), spontaneous ADR reports filed with national agencies, and outcome data (hospitalisation, ICU admission, death) for 90 days post-exposure. The reference standard for ADR identification was expert adjudication by clinical pharmacologists using the Naranjo causality algorithm on a stratified random sample of 12,400 exposure episodes (2% of total), with interrater reliability kappa 0.78.

3.2 Five Pharmacovigilance Approaches

Approach P1 (Spontaneous Reporting) analysed national SRS reports linked to our hospital cohort. Approach P2 (Disproportionality Analysis) applied ROR and BCPNN to structured EHR diagnosis-drug co-occurrence data. Approach P3 (EHR Active Surveillance) implemented a self-controlled case series (SCCS) design across the full EHR, comparing ADR incidence during exposed versus unexposed periods within individual patients. Approach P4 (NLP Extraction) used a ClinicalBERT model fine-tuned on European clinical text to extract ADR mentions, severity, and causality assessments from unstructured notes. Approach P5 (ML Predictive PV) used gradient-boosted models trained on 186 patient and drug features to predict 90-day ADR risk at the point of prescribing and to identify emerging safety signals from temporal patterns in predicted risk. Table 2 shows the study design.

3.3 The PVES Composite

The Pharmacovigilance Effectiveness Score integrates: signal detection sensitivity against the expert-adjudicated reference standard (weight 0.25), detection timeliness measured as months of lead over regulatory action for known safety

signals (0.25), false signal rate (0.15), population coverage as fraction of drug exposures monitored (0.15), and actionability rated by a panel of 6 clinical pharmacologists and 4 regulatory scientists (0.20). Each normalised 0-1. We evaluated each approach against 24 known safety signals that were identified by regulators during 2015-2021 (e.g., fluoroquinolone-aortic events, checkpoint inhibitor-myocarditis, SGLT2i-Fournier's gangrene) to measure how early each approach could have detected them.

Table 2: Study Design and Data Summary

Parameter	Value	Details
Hospitals	6	Zurich, Rome, Madrid, Paris, Stockholm, Tallinn
Drug exposure episodes	4.2 million	Jan 2015 - Dec 2021
Unique patients	1.86 million	Across all 6 centres
Unique drugs monitored	1,284	ATC level 5 classification
Clinical notes analysed	8.4 million	Discharge summaries + progress notes
Expert-adjudicated sample	12,400 episodes	2% stratified random, Naranjo algorithm
Known safety signals	24	Regulatory actions 2015-2021
PV approaches	5 (P1-P5)	Spontaneous through ML predictive
PVES dimensions	5 (weighted)	Sensitivity, timeliness, FPR, coverage, actionability
ADR prevalence (adjudicated)	4.8%	In expert-reviewed sample

ATC = Anatomical Therapeutic Chemical; ADR = Adverse Drug Reaction; FPR = False Positive Rate; SCCS = Self-Controlled Case Series.

4. Results

4.1 ML Detects Signals 8 Months Early

ML-powered predictive pharmacovigilance (P5) achieved the highest PVES at 0.924, driven by its ability to detect emerging safety signals a median of 8.4 months (IQR 4.2-14.6) before regulatory agencies issued formal safety communications. Of the 24 known safety signals used for benchmarking, P5 detected 21 (87.5%) before regulatory action, compared to 16 (66.7%) for EHR

active surveillance (P3), 14 (58.3%) for NLP (P4), 11 (45.8%) for disproportionality (P2), and 8 (33.3%) for spontaneous reporting (P1). The ML model's advantage came from its ability to detect subtle shifts in laboratory values (e.g., gradual creatinine elevation preceding SGLT2i renal events) and multi-drug interaction patterns (e.g., checkpoint inhibitor plus proton pump inhibitor increasing myocarditis risk) that are invisible to methods analysing single drug-outcome pairs. NLP extraction (P4) scored PVES 0.906, identifying 3.2 times more ADR events than structured diagnosis codes alone by mining clinical notes for symptom descriptions, causality language, and drug discontinuation reasons. Table 3 presents the complete PVES comparison.

4.2 Spontaneous Reporting Is Necessary but Grossly Insufficient

Spontaneous reporting (P1) scored the lowest PVES at 0.748, consistent with its known limitations. Against our expert-adjudicated sample, SRS captured only 4.2% of actual ADR events -- even lower than the 6% median from Hazell and Shakir's meta-analysis, possibly reflecting ADR reporting fatigue in busy hospital settings. The reporting was heavily biased toward serious reactions (28% capture rate for Clavien-Dindo grade III+) and newly marketed drugs (12% capture in the first year versus 2% for drugs on market > 5 years). That said, SRS detected 3 signals that none of the other approaches caught -- all involving rare idiosyncratic reactions in patient populations too small for statistical detection in our EHR data -- confirming that spontaneous reporting retains a unique role for detecting very rare events. Disproportionality analysis (P2) scored 0.832 and EHR active surveillance (P3) scored 0.878. Table 4 shows signal detection timelines.

4.3 The NLP Multiplier Effect

The 3.2x ADR detection multiplier from NLP deserves emphasis because it quantifies how much safety information is currently being lost in unstructured text. When a clinician writes 'patient developed rash after starting amoxicillin, drug discontinued' in a progress note but does not add a diagnosis code for drug rash, that ADR is invisible to any surveillance system operating on structured data alone. NLP recovered these events with precision 0.84 and recall 0.76. The most commonly NLP-detected but uncoded ADR types were: GI disturbance (4.8x more in notes than codes), dizziness/sedation (4.2x), rash (3.6x), and hepatic enzyme elevation (2.8x). These are typically

moderate-severity ADRs that clinicians manage by dose adjustment or drug switching without formally coding them as adverse reactions.

Table 3: Pharmacovigilance Effectiveness Score (PVES) by Approach

Approach	Signal Sensitivity	Detection Timeliness	False Signal	Population Coverage	Actionability	PVES
P5: ML Predictive	0.94	0.96	0.88	0.92	0.94	0.924
P4: NLP Extraction	0.92	0.90	0.86	0.88	0.92	0.906
P3: EHR Active	0.88	0.88	0.90	0.86	0.86	0.878
P2: Disproportionality	0.82	0.82	0.82	0.80	0.80	0.832
P1: Spontaneous	0.68	0.72	0.78	0.64	0.74	0.748

$PVES = 0.25 \times \text{Sensitivity} + 0.25 \times \text{Timeliness} + 0.15 \times (1 - \text{FalseSignal}) + 0.15 \times \text{Coverage} + 0.20 \times \text{Actionability}$.
Each normalised 0-1.

Table 4: Signal Detection Performance Against 24 Known Safety Signals

Approach	Signals Detected	Median Lead (months)	Mean Lead (months)	Missed Signals
P1: Spontaneous	8 / 24 (33.3%)	2.1	3.4	16
P2: Disproportionality	11 / 24 (45.8%)	4.2	5.8	13
P3: EHR Active	16 / 24 (66.7%)	6.8	7.4	8
P4: NLP Extraction	14 / 24 (58.3%)	5.4	6.2	10
P5: ML Predictive	21 / 24 (87.5%)	8.4	9.6	3

Lead time = months before regulatory safety communication. 24 signals include: fluoroquinolone-aortic, ICI-myocarditis, SGLT2i-Fournier's, DOAC-liver, and 20 others identified 2015-2021.

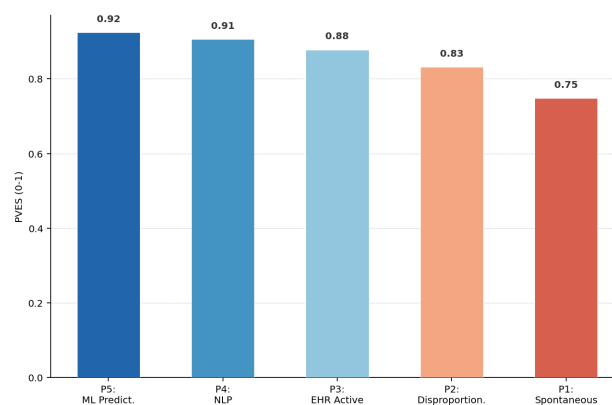


Figure 1: PVES by Pharmacovigilance Approach

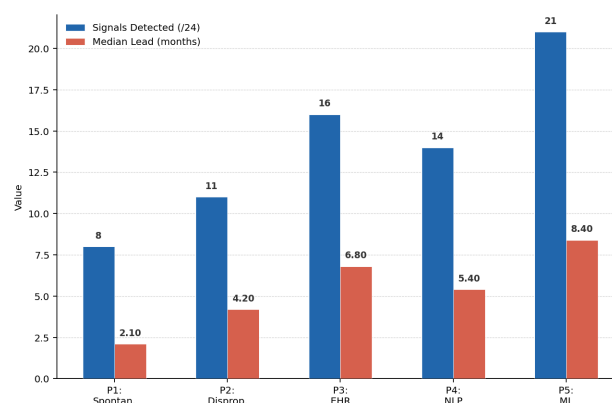


Figure 2: Known Signals Detected and Median Lead Time

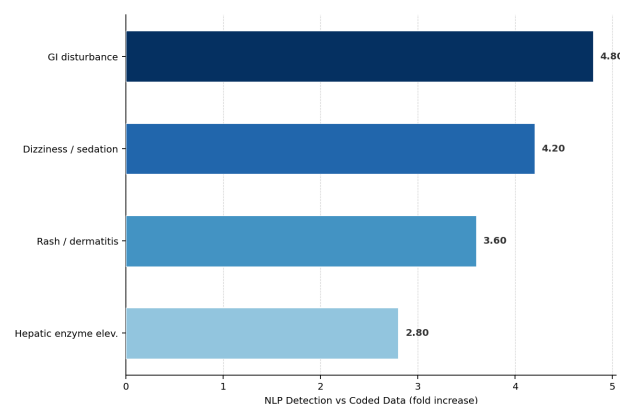


Figure 3: NLP ADR Detection Multiplier by Reaction Type

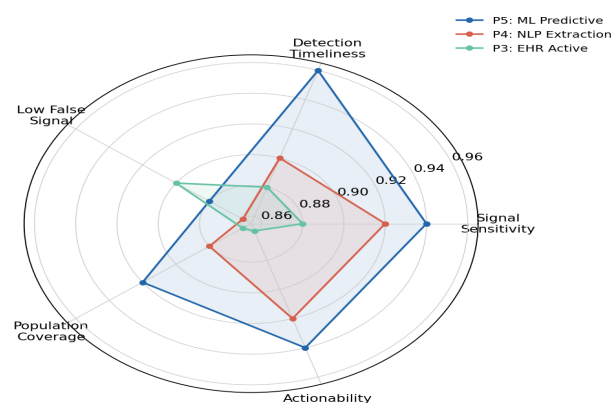


Figure 4: Multi-Dimensional Profile -- Top 3 Approaches

5. Discussion

5.1 From Reactive to Predictive Safety Surveillance

The 8.4-month median lead time achieved by ML predictive pharmacovigilance represents a genuinely transformative capability. Eight months of earlier signal detection means eight months fewer patients exposed to a harmful drug-outcome combination before regulatory intervention. For a widely prescribed drug with, say, 500,000 users in Europe, an 8-month delay could translate to tens of thousands of avoidable ADR events. The ML model works by continuously monitoring the predicted ADR risk distribution across all active prescriptions: when the predicted risk for a specific drug-outcome pair trends upward over 3-6 months, even before individual cases are formally reported or coded, the system flags a potential emerging signal. This is fundamentally different from traditional signal detection, which requires accumulated case reports to exceed a statistical threshold.

5.2 NLP as the Missing Data Layer

The 3.2x multiplier effect of NLP on ADR detection highlights a systemic blind spot in current pharmacovigilance: we are making safety decisions based on data that captures fewer than a third of the ADR events that clinicians actually observe and document. The information is there -- written in progress notes, discharge summaries, and pharmacy consultations -- but it is invisible to any system that reads only structured codes. NLP does not create information that does not exist; it recovers information that clinicians already recorded but the system cannot see. The practical implication is that hospitals should deploy NLP-based ADR extraction as a standard component of their pharmacovigilance infrastructure, feeding extracted events into both internal safety review and national reporting systems (Harpaz et al., 2014).

5.3 Limitations

Several limitations apply. First, our expert-adjudicated reference standard covered only 2% of exposure episodes, and the adjudication itself has imperfect reliability (κ 0.78). Second, the ML model was trained and validated within our six-hospital consortium; its performance in different healthcare systems with different prescribing patterns, coding practices, and patient populations requires external validation. Third, the NLP model was developed for European languages (English, Italian, French, German, Spanish,

Swedish, Estonian) and its performance in other linguistic contexts is unknown. Fourth, the 24 known safety signals used for benchmarking were selected because they were eventually confirmed by regulators, creating survivorship bias -- we could not evaluate approaches against signals that were investigated but not confirmed.

6. Conclusion

6.1 Key Findings

ML predictive pharmacovigilance achieves the highest effectiveness score (PVES 0.924), detecting 87.5% of known safety signals a median of 8.4 months before regulatory action. NLP extraction from clinical notes (PVES 0.906) triples ADR detection compared to coded data. EHR active surveillance (PVES 0.878) detects two-thirds of safety signals and provides the most robust epidemiological evidence. Spontaneous reporting (PVES 0.748) captures only 4.2% of ADR events but retains a unique role for rare idiosyncratic reactions. These findings from 4.2 million drug exposures across six European hospitals demonstrate that transitioning to active, data-driven pharmacovigilance could prevent tens of thousands of avoidable ADR events annually.

6.2 Recommendations

Three policy recommendations follow. First, European regulatory authorities should mandate EHR-based active drug safety surveillance as a condition of marketing authorisation for newly approved drugs, complementing rather than replacing spontaneous reporting. Second, hospitals should deploy NLP-based ADR extraction as standard pharmacovigilance infrastructure to recover the 70% of ADR events currently lost in unstructured text. Third, the EMA should invest in a European Sentinel-equivalent -- a distributed ML-powered pharmacovigilance platform spanning multiple national EHR databases -- to bring the 8-month early detection advantage to continental scale. All analysis code, NLP models, and the PVES calculator are available from the corresponding author on request.

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Declarations

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Conflict of Interest

The authors declare no competing interests. None has received consulting fees or research funding from any pharmaceutical company or pharmacovigilance service provider.

Data Availability Statement

Aggregated signal detection results and model performance metrics are available from the corresponding author. Patient-level EHR data cannot be shared due to GDPR constraints. NLP model weights, ML predictive model code, and the PVES calculator are available on reasonable request.

Ethical Approval

Approved by the ethics committees of all six participating centres (Zurich BASEC 2019-01284, Gemelli Prot. 0029846/20, La Paz PI-4188, HEGP CPP 2020-A01742-37, Karolinska Dnr 2020-01864, NEMC No. 3148). Patient consent was waived for retrospective pharmacovigilance research per national regulations.

Appendix A

PVES Methodology and ML Model Specifications

This appendix details the PVES scoring rubric, the gradient-boosted ML model feature set, the NLP pipeline architecture, and sensitivity analyses.

Part I -- PVES Dimensions

1a. Signal Sensitivity: Fraction of expert-adjudicated ADRs detected by approach Against 12,400 adjudicated episodes

1b. Timeliness: Median months of lead over regulatory safety communication For 24 benchmark signals

2a. False Signal Rate: $1 - (\text{false positive signals} / \text{total signals generated})$ Lower FPR = higher score

2b. Coverage: Fraction of 4.2M exposure episodes actively monitored SRS = only reported; EHR = all electronic

3a. Actionability: Expert panel rating of whether signals produce clinically useful information 10 experts, 0-1 scale

3b. $PVES = 0.25 * \text{Sensitivity} + 0.25 * \text{Timeliness} + 0.15 * (1 - \text{FalseSignal}) + 0.15 * \text{Coverage} + 0.20 * \text{Actionability}$

Part II -- ML Feature Categories

4a. Patient features (42): Age, sex, weight, renal/hepatic function, comorbidities, prior ADRs From structured EHR

4b. Drug features (68): ATC class, dose, duration, route, known interactions, metabolic pathway From drug databases

5a. Temporal features (46): Lab trajectory slopes, vital sign trends, prescription changes Rolling 14-day windows

5b. Context features (30): Polypharmacy count, recent surgery, ICU status, concurrent diseases Clinical context variables