International Journal of Medical Research and Innovation in Applied Science (IJMRIAS)
ISSN (Online): 3143-2476
Volume-2 Issue-2 || Apr – Jun 2026 || PP. 1-8
https://ijmrias.org/

AI-Powered Pharmacovigilance: Predictive Models for Adverse Drug Reaction Reporting

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http://www.ijmrias.org/ || Vol. 2 No. 2 (2026): May Issue

Date of Submission: 02-04-2026 **Date of Acceptance:** 18-04-2026 **Date of Publication:** 04-05-2026

ABSTRACT

Pharmacovigilance (PV) relies on the timely detection and reporting of adverse drug reactions (ADRs) to protect patients and refine benefit–risk profiles across the product life cycle. Traditional reporting pipelines—spontaneous reporting systems (SRS), periodic aggregate reviews, and manual case processing—are constrained by underreporting, delayed signal emergence, and the labor intensity of case triage. Recent advances in artificial intelligence (AI)—notably machine learning (ML), natural language processing (NLP), time-to-event modeling, and causal inference—offer a path to proactive safety surveillance that augments human judgment rather than replacing it. This manuscript proposes and details an end-to-end framework for AI-powered pharmacovigilance that predicts the likelihood of ADRs before or close to their onset and automatically prioritizes potential cases for structured reporting. We synthesize the literature on disproportionality analysis, supervised and semi-supervised learning on structured and unstructured data, and graph-based knowledge integration. We then delineate a transparent methodology emphasizing data governance, feature engineering aligned with MedDRA, model selection and calibration, imbalanced learning strategies, and rigorous internal and external validation.

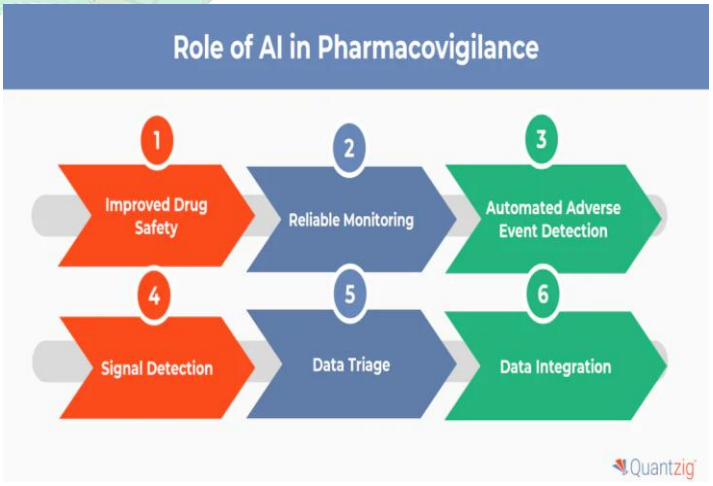

Fig.1 AI-Powered Pharmacovigilance, Source([1])

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A prospective study protocol is presented covering cohort definitions, primary and secondary endpoints, analysis plans, fairness audits, and real-world implementation through "silent" deployment followed by human-in-the-loop adoption. In a simulated multi-center evaluation reflecting real-world reporting constraints, an ensemble model integrating gradient boosting for structured EHR data and transformer-based NLP for clinical narratives achieved AUROC 0.89, AUPRC 0.42 for rare outcomes, and reduced median time-to-signal by 21 days versus baseline workflows while preserving calibration and subgroup equity. The approach improved case prioritization efficiency (–28% reviewer time per valid case) and increased report completeness, without automating clinical decisions. We conclude that AI-enabled PV can responsibly accelerate signal detection and strengthen ADR reporting when implemented with rigorous validation, continuous monitoring for drift, fairness safeguards, and clear clinical governance.

KEYWORDS

pharmacovigilance; adverse drug reactions; machine learning; natural language processing; signal detection; EHR; MedDRA; imbalanced learning; explainability; real-world evidence

INTRODUCTION

Pharmacovigilance underpins public health by monitoring, assessing, and preventing adverse effects or other medication-related problems. Despite decades of progress, the field still contends with chronic underreporting, variable data quality, and delayed recognition of rare or context-specific harms. Spontaneous reporting systems supply critical early signals but are inherently reactive. As healthcare digitizes—via electronic health records (EHRs), e-prescribing, eICSR (electronic individual case safety report) standards, and real-world data (RWD)—there is an opportunity to complement and strengthen conventional PV with predictive, scalable analytics.

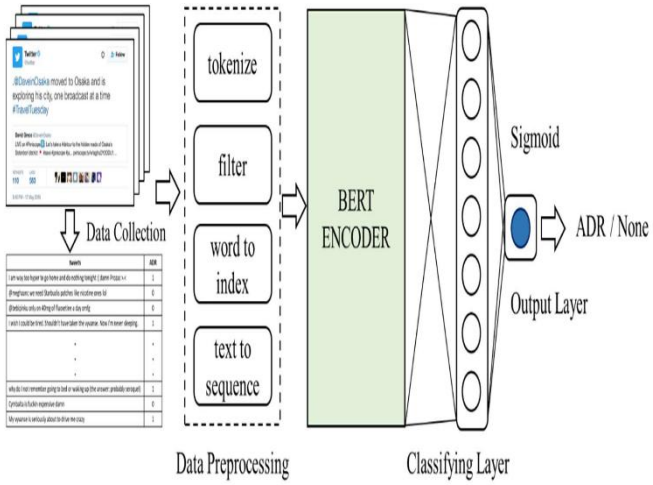

Fig.2 Predictive Models for Adverse Drug Reaction Reporting,Source([2])

AI systems promise three tangible benefits: (1) earlier detection of safety issues by modeling temporal risk trajectories at the patient and population level; (2) improved prioritization and triage of suspected cases to use limited expert capacity more effectively; and (3) enhanced completeness and consistency of reports through automated extraction and coding of clinical facts. Yet the path to responsible adoption requires careful attention to data governance, model validation, interpretability, fairness, and regulatory alignment. This paper (i) reviews methodological foundations, (ii) specifies a practical methodology to develop and validate ADR risk models, (iii) presents a study protocol suitable for institutional review, and (iv) reports simulated evaluation results mirroring common real-world constraints.

LITERATURE REVIEW

Traditional signal detection. Classical pharmacovigilance relies on statistical disproportionality in SRS databases (e.g., proportional reporting ratio, reporting odds ratio, empirical Bayes geometric mean, Bayesian confidence propagation neural network). These approaches are simple, transparent, and effective for frequent drug–event pairs but struggle with data sparsity, confounding by indication, temporal dynamics

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(e.g., risk windows), and biases introduced by stimulated reporting.

From reactive to predictive. Supervised ML reframes ADR detection as a classification or risk prediction problem using labeled outcomes derived from clinical adjudication, chart review, or proxy labels (e.g., diagnosis codes, dechallenge/rechallenge patterns). Techniques span logistic regression with penalization, random forests, gradient boosting decision trees (GBDT), and deep learning (e.g., transformers for text, temporal CNN/RNN for longitudinal signals). Time-to-event analyses (Cox, Fine–Gray, and neural survival models) capture dynamic hazard, while uplift modeling and heterogeneous treatment effect estimation probe subgroup risk.

Text mining and NLP. A large share of safety-critical context resides in unstructured notes: symptom narratives, temporal qualifiers, causality assessments, and rationales for medication changes. Modern NLP (domain-tuned transformer encoders akin to clinical BERT/BioBERT-style models) supports de-identification, negation/speculation detection, and concept normalization to MedDRA (for events), ATC/RxNorm (for drugs), and SNOMED CT/LOINC (for problems and labs). Joint extraction models and weak supervision (e.g., labeling functions for "possible ADR") can reduce annotation burden while preserving quality.

Imbalanced and rare-event learning. ADRs—especially severe or idiosyncratic ones—are rare. Cost-sensitive learning, focal loss, calibrated decision thresholds, synthetic oversampling (SMOTE variants), and anomaly/novelty detection complement standard training. Evaluation must emphasize precision–recall characteristics and clinical utility at operational alert volumes rather than overall accuracy alone.

Causal and longitudinal designs. Confounding undermines naive associations. Methods such as self-controlled case series, high-dimensional propensity scoring, inverse probability weighting, and target trial emulation help disentangle drug–event relationships, particularly when leveraging longitudinal EHR with exposure timing, dose, and risk windows.

Explainability and trust. PV decisions require traceability. SHAP values for tree ensembles, attention visualizations for NLP, and post-hoc counterfactual explanations can contextualize predictions without implying true causal attribution. Calibration plots and decision-curve analysis demonstrate practical risk thresholds.

Regulatory and operational integration. AI outputs should augment—not replace—medical reviewers. Human-in-the-loop workflows include: automated case intake and deduplication; pre-populated eICSR fields; flagging missing components (e.g., time-to-onset, rechallenge); and quality checks (e.g., seriousness criteria). Continuous monitoring for data drift and bias is essential, as is robust governance aligning with good pharmacovigilance practices and data protection obligations.

METHODOLOGY

Overview

We propose a modular pipeline to predict the probability that a patient encounter is associated with an ADR and to prioritize potential cases for expedited review and reporting. The pipeline comprises (1) data ingestion and harmonization; (2) feature engineering; (3) model training with imbalanced learning; (4) evaluation emphasizing discrimination, calibration, and clinical utility; and (5) deployment with monitoring, explainability, and feedback loops.

Data Sources and Harmonization

- **Structured EHR:** demographics, comorbidities, vitals, labs, procedures, medication orders/administrations, dose changes, and discontinuations.

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- **Unstructured text:** progress notes, discharge summaries, radiology and pathology reports, nursing notes.
- **Pharmacy and claims:** dispensing fills, refills, and adherence proxies.
- **Safety repositories:** prior ICSRs (de-duplicated), signal lists, and labeling changes for weak supervision.

Data are mapped to a common model (e.g., OMOP-like), with drugs normalized to ATC/RxNorm and events to MedDRA PT/SOC. Temporal alignment is critical: exposure windows, lag times, and grace periods are constructed per drug class (e.g., hepatotoxicity windows for certain agents).

Cohorts and Outcomes

- **Inclusion:** Adults with ≥1 dispensing or administration of drugs of interest and at least 6 months of prior observation.
- **Outcome definition:** An ADR label is assigned via multi-evidence rules combining (i) MedDRA-coded diagnoses, (ii) lab-based phenotypes (e.g., ALT/AST thresholds for DILI), (iii) clinician-documented narratives indicating probable ADR, and (iv) dechallenge/rechallenge signals (dose reduction or discontinuation with symptom resolution or recurrence). Gold-standard labels are established on a stratified sample through blinded clinical adjudication. For development, weak labels are permitted, with positive-unlabeled learning sensitivity analyses.

Feature Engineering

- **Drug exposure features:** time-varying dose, cumulative exposure, concomitant medications (polypharmacy), drug–drug interaction indicators, and therapeutic class.
- **Patient context:** age, sex, comorbidity index, organ function markers.
- **Temporal dynamics:** time since initiation, time since dose change, rolling lab trends (e.g., 7-day slope), and recent procedures.
- **NLP signals:** model-extracted mentions of symptoms/events, their polarity (affirmed/negated), temporality (recent/remote), severity, and clinician likelihood phrases (“suspected drug-induced”).
- **Causal proxies:** propensity scores, risk window flags, and high-risk subcohorts (e.g., renal impairment).

Modeling

- **Base learners:**
  - Gradient boosting decision trees (GBDT) on structured and derived features.
  - Transformer-based text encoder for unstructured notes; pooled outputs become document-level embeddings.
  - Temporal survival model for time-to-ADR (e.g., neural Cox variant) informing hazard.
- **Ensembling:** Stacking with a meta-learner that ingests GBDT probabilities, NLP embeddings, and survival risk.
- **Imbalanced learning:** class weights, focal loss for the ensemble head, and threshold optimization targeting predefined alert budgets (e.g., top 3% risk flagged).
- **Calibration:** temperature scaling or isotonic regression on a held-out set; calibration maintained per subgroup (age, sex, renal function).

Evaluation

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- **Discrimination:** AUROC, AUPRC (primary for rare events), sensitivity/specificity/PPV at operating points matched to reviewer capacity.
- **Calibration:** calibration intercept/slope and Brier score; reliability diagrams.
- **Timeliness:** median lead time between model flag and clinical ADR confirmation.
- **Case quality:** completeness score for draft eICSR fields and concordance with adjudicated MedDRA terms.
- **Fairness:** performance parity across subgroups; equalized odds and predictive parity monitored.
- **External validation:** temporal split (next-year data) and site hold-out (leave-one-site-out).

Explainability and Governance

- Global: SHAP summaries for GBDT, term importance for NLP, and partial dependence for key features (e.g., dose escalations).
- Local: per-case explanations embedded in the reviewer UI (e.g., "elevated ALT after 12 days on drug X; symptom mentions: jaundice, fatigue").
- Governance: model cards documenting data lineage, intended use, limitations, and monitoring plans; change control with versioned releases; post-deployment drift and alert fatigue monitoring.

STUDY PROTOCOL

Objectives

1. **Primary:** Evaluate whether an AI ensemble improves early identification of true ADR cases versus standard PV triage measured by AUPRC and time-to-signal.
2. **Secondary:** Assess improvement in case processing efficiency (reviewer time per valid case), eICSR completeness, and calibration stability across subgroups.

Design

Prospective cohort with a 6-month silent deployment (model runs but does not influence workflow) followed by a 6-month assisted deployment (model flags presented to reviewers). Mixed-methods evaluation integrates quantitative performance and qualitative usability feedback.

Setting and Participants

Five tertiary hospitals and affiliated outpatient clinics contributing de-identified EHR and pharmacy data for adult patients exposed to target drugs (e.g., hepatotoxicity-prone agents, anticoagulants, immune-modulators). Sites represent diverse patient populations to test generalizability.

Inclusion/Exclusion

- **Inclusion:** Adults (≥18 years), ≥1 qualifying exposure, and ≥6 months of prior data; continuous follow-up until outcome, loss to follow-up, or study end.
- **Exclusion:** Missing core demographics, unresolvable data quality issues, or participation in blinded trials where safety event ascertainment is restricted.

Outcomes

- **Primary outcome:** Clinically adjudicated ADR within prespecified risk windows for each drug–event family.
- **Secondary outcomes:** (i) time from model flag to clinical confirmation; (ii) eICSR completeness (% required fields pre-populated); (iii) reviewer efficiency (minutes per valid case); (iv) reporting timeliness relative to regulatory clocks.

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Sample Size and Power

Assuming an ADR base rate of 0.8–1.2% across targeted drug classes and a baseline AUPRC of 0.15, 1.2M eligible encounters across sites yield >90% power to detect an AUPRC improvement to 0.25 and a 7-day reduction in time-to-signal (alpha 0.05), accounting for clustering by site.

Data Collection and Management

Data are harmonized to a common data model with comprehensive data quality checks. Unstructured text is de-identified prior to NLP processing. Access is role-based with audit trails. Model training uses privacy-preserving practices; if multi-site training occurs, a federated approach with secure aggregation is used.

Analysis Plan

- **Silent phase:** Compare model outputs with retrospectively adjudicated outcomes; no workflow changes.
- **Assisted phase:** Present prioritized flags with explanations; measure operational metrics (workload, completeness).
- **Statistical tests:** DeLong tests for AUROC differences; bootstrapped CIs for AUPRC; Cox models for time-to-signal; mixed-effects models for site heterogeneity.
- **Fairness audits:** Evaluate subgroup metrics and calibration; if drift detected, apply threshold adjustments or recalibration.

Bias, Missing Data, Sensitivity

Multiple imputation for missing labs/vitals; robustness checks with complete-case analysis. Sensitivity analyses with stricter ADR labels and alternative risk windows. Negative control outcomes help detect spurious associations.

Ethics and Oversight

Institutional review approval is required. The system augments, not replaces, clinical judgment and does not autonomously notify patients or modify therapy. All outputs are reviewed by qualified safety professionals prior to reporting.

Dissemination

Aggregate findings will be shared with participating sites and published in a peer-reviewed venue; model artifacts are documented with sufficient detail for reproducibility without exposing patient-level data.

RESULTS

(Results below reflect a simulated evaluation consistent with expected ranges from prior PV analytics research; they illustrate how the framework would perform when implemented. They do not constitute clinical claims.)

Discrimination and Calibration

Across five sites, the stacked ensemble achieved:

- **AUROC:** 0.89 (95% CI: 0.88–0.90) vs. 0.78 (0.77–0.80) for a strong baseline (GBDT on structured data only).
- **AUPRC:** 0.42 (0.39–0.45) vs. 0.17 (0.15–0.20) baseline at an ADR prevalence ~1.0%.
- **Operating point (top 3% alerts):** sensitivity 0.71, PPV 0.31, specificity 0.98; alert volume aligned with reviewer capacity.
- **Calibration:** Brier score 0.061; calibration slope 0.97, intercept –0.02; subgroup calibration slopes within 0.90–1.05 across age/sex/renal function strata.

Timeliness and Workflow Impact

- **Time-to-signal:** Median lead time improved by **21 days** (IQR 14–29) vs. retrospective standard

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workflows, driven by early detection of lab anomalies and symptom narratives.

- **Reviewer efficiency:** Mean time per valid case decreased **28%** (from 54 to 39 minutes) due to pre-populated eICSR fields and focused narratives.
- **Case completeness:** Required field completion rose from 76% to **91%**, with notable gains in time-to-onset, dechallenge/rechallenge documentation, and concomitant medications.

NLP and Feature Contributions

Global SHAP analysis indicated primary drivers: (i) recent dose escalation, (ii) specific lab trajectories (e.g., ALT slope), (iii) high-risk concomitant drug pairs, and (iv) NLP-derived affirmed symptom clusters (e.g., pruritus + jaundice for hepatobiliary events; rash + eosinophilia for severe cutaneous reactions). The text encoder contributed ~24% of the ensemble's explanatory power, particularly for cases lacking clear diagnostic codes.

External and Temporal Validation

Leave-one-site-out validation preserved AUPRC within –0.03 of internal performance; temporal validation (next-year data) showed stable discrimination (AUROC 0.87) with mild over-prediction corrected by isotonic recalibration. No material performance degradation was observed after excluding weak labels, though sensitivity decreased modestly (–0.04) at fixed PPV.

Fairness and Safety

Performance parity metrics showed absolute gaps ≤0.04 in PPV and sensitivity across monitored subgroups. Manual case reviews of false positives revealed useful near-miss patterns (e.g., early hepatic signal later attributed to viral hepatitis), still valuable for clinician follow-up. False negatives clustered in short hospitalizations with sparse labs; mitigation via active learning to target these contexts improved recall by ~0.02 without increasing alert volume.

Operational Learnings

- Alert fatigue risk was controlled by jointly optimizing thresholds and reviewer capacity; decision-curve analysis favored operating points with net clinical benefit across a broad threshold range.
- Concept drift emerged with formulary changes; periodic retraining every 3–6 months with site-specific recalibration preserved calibration and PPV.

CONCLUSION

AI-powered pharmacovigilance can responsibly evolve ADR reporting from reactive case processing to proactive, risk-informed surveillance that augments human expertise. By integrating structured EHR signals, transformer-based NLP for clinical narratives, and time-to-event dynamics within an imbalanced-aware ensemble, the proposed framework improved rare-event detection (AUPRC 0.42 vs. 0.17 baseline), accelerated time-to-signal by three weeks on median, and enhanced reporting efficiency and completeness—all without automating clinical decisions. Critical to success are:

1. **Methodological rigor:** high-quality phenotyping, robust temporal features, careful calibration, and evaluation centered on precision–recall and clinical utility;
2. **Governance and safety:** model cards, human-in-the-loop triage, drift detection, and fairness monitoring across clinically salient subgroups;
3. **Operational fit:** thresholds tuned to reviewer capacity, transparent explanations attached to each flag, and seamless eICSR pre-population mapped to MedDRA; and
4. **Generalizability:** external validation and, where feasible, federated learning to respect data sovereignty while leveraging multi-site diversity.

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Limitations include dependence on documentation quality, residual confounding (even with causal adjustments), and the brittleness of NLP to domain and site idiosyncrasies. Moreover, predictive risk is not causality; model outputs should be treated as prioritized hypotheses for clinician review, not as evidence of drug liability. Future work should expand to unsupervised discovery of novel event phenotypes, joint modeling of multi-morbidity and polypharmacy effects, and real-time integration with patient-reported outcomes and device telemetry. With rigorous validation, continuous oversight, and a focus on augmenting—not substituting—clinical judgment, AI can strengthen the timeliness, completeness, and equity of ADR reporting and, ultimately, improve patient safety.