

Hybrid Evidence-Based Recalibration for Drug-Drug Interaction Severity Classification

Methods, Validation, and Clinical Alignment

Anonymous Authors

February 2026

Abstract

Zero-shot natural language inference models have demonstrated remarkable capability in classifying drug-drug interaction (DDI) severity without task-specific training. However, these models frequently exhibit over-classification bias, particularly toward high-severity categories, resulting in distributions that deviate substantially from clinical expectations. We present a hybrid evidence-based recalibration framework that combines (1) clinical text marker analysis, (2) confidence-weighted adjustment, and (3) pharmacological risk profiling to align zero-shot predictions with literature-derived severity distributions. Applied to 759,774 cardiovascular and antithrombotic DDI pairs from DrugBank, our method reduces contraindicated classifications from 56.9% to 1.9% while maintaining 100% sensitivity for clinically validated high-risk combinations. The recalibrated distribution achieves strong concordance with clinical literature targets (Contraindicated: 5%, Major: 25%, Moderate: 60%, Minor: 10%) and improves mean prediction confidence by 18.4%.

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1 Introduction

1.1 Background and Motivation

Drug-drug interactions (DDIs) represent a significant source of preventable adverse drug events, accounting for approximately 3–5% of hospital admissions and contributing substantially to healthcare costs. Accurate severity classification of DDIs is essential for clinical decision support systems, enabling healthcare providers to prioritize interventions and balance therapeutic benefits against interaction risks.

Zero-shot classification approaches, particularly those based on natural language inference (NLI) models such as BART-MNLI, have emerged as promising methods for DDI severity prediction. These models can classify interactions without requiring labeled training data by framing severity prediction as an entailment task. However, a critical limitation of zero-shot approaches is their tendency toward over-classification, particularly favoring high-severity categories when interaction descriptions contain clinical terminology.

1.2 Problem Statement

Analysis of zero-shot severity predictions on 759,774 DDI pairs from DrugBank revealed severe distribution imbalance:

- **Contraindicated:** 56.9% (predicted) vs. \sim 5% (literature)
- **Major:** 43.0% (predicted) vs. \sim 25% (literature)
- **Moderate:** $<0.1\%$ (predicted) vs. \sim 60% (literature)
- **Minor:** 0.1% (predicted) vs. \sim 10% (literature)

This over-classification phenomenon, while erring on the side of caution, diminishes clinical utility by overwhelming practitioners with false-positive high-severity alerts, contributing to alert fatigue.

1.3 Contributions

This work presents:

1. A **hybrid recalibration framework** combining multiple evidence sources
2. **Clinical text marker analysis** based on pharmacovigilance terminology
3. **Drug class risk profiling** for pharmacologically-informed adjustment
4. **Comprehensive validation** against clinical benchmarks

2 Methods

2.1 Overview

The Hybrid Evidence-Based Severity Recalibration (HEBSR) framework employs a weighted ensemble of three complementary scoring mechanisms:

$$S_{\text{final}} = w_m \cdot S_{\text{marker}} + w_c \cdot S_{\text{confidence}} + w_d \cdot S_{\text{drug_class}} \quad (1)$$

where $w_m = 0.4$, $w_c = 0.3$, and $w_d = 0.3$ represent empirically-tuned weights for marker analysis, confidence adjustment, and drug class scoring, respectively.

2.2 Component 1: Clinical Text Marker Analysis

2.2.1 Marker Taxonomy

We developed a hierarchical taxonomy of clinical text markers derived from FDA labeling guidelines, pharmacovigilance literature, and the DrugBank interaction description corpus. Markers are stratified into four severity tiers:

Contraindicated Markers ($S = 4.0$) Indicators of immediately life-threatening outcomes:

- Cardiac: torsades de pointes, QTc prolongation, cardiac arrest
- Neurological: serotonin syndrome, neuroleptic malignant syndrome
- Fatal: fatal, death, lethal

Major Markers ($S = 3.2$) Serious adverse events requiring clinical intervention:

- Hemorrhagic: bleeding, hemorrhage, gastrointestinal bleeding
- Metabolic: hyperkalemia, hypoglycemia, rhabdomyolysis
- Organ toxicity: renal failure, hepatotoxicity, agranulocytosis

Moderate Markers ($S = 2.0$) Pharmacokinetic/pharmacodynamic effects requiring monitoring:

- Blood pressure: hypertension, hypotension
- PK effects: serum concentration increase/decrease
- Metabolic: metabolism inhibition/induction

Minor Markers ($S = 1.5$) Effects of limited clinical significance:

- therapeutic efficacy decrease (without mechanism)
- Generic pharmacokinetic statements

2.2.2 Marker Detection Algorithm

The marker detection process employs prioritized pattern matching with longest-match semantics. The algorithm processes markers in order of decreasing severity:

1. Check contraindicated markers first (score = 4.0)
2. Check major markers sorted by length, longest first (score = 3.2)
3. Check moderate markers (score = 2.0)
4. Check minor markers (score = 1.5)
5. Default score = 1.6 if no marker found

2.3 Component 2: Confidence-Weighted Zero-Shot Adjustment

The original zero-shot prediction is converted to a numeric score and adjusted based on prediction confidence:

$$S_{\text{confidence}} = \begin{cases} 3.0 & \text{if } \hat{y} = \text{Contraindicated} \wedge c < \tau_c \\ 2.5 & \text{if } \hat{y} \in \{\text{Contraindicated}, \text{Major}\} \wedge c < \tau_m \\ \phi(\hat{y}) & \text{otherwise} \end{cases} \quad (2)$$

where \hat{y} is the predicted label, c is the prediction confidence, $\tau_c = 0.65$ and $\tau_m = 0.50$ are confidence thresholds, and $\phi : \mathcal{Y} \rightarrow \{1, 2, 3, 4\}$ maps severity labels to numeric scores:

$$\phi(\hat{y}) = \begin{cases} 4 & \hat{y} = \text{Contraindicated} \\ 3 & \hat{y} = \text{Major} \\ 2 & \hat{y} = \text{Moderate} \\ 1 & \hat{y} = \text{Minor} \end{cases} \quad (3)$$

This component penalizes low-confidence high-severity predictions, effectively implementing skepticism for uncertain contraindication calls.

2.4 Component 3: Drug Class Risk Profiling

Pharmacological class membership informs severity adjustment through known high-risk drug combinations:

Table 1: Drug Class Risk Categories

Risk Level	Drug Classes	Score
Very High	MAOIs (both drugs)	4.0
High	Anticoagulants, QT-prolonging (overlap)	3.5
Elevated	Any high-risk overlap	3.0
Moderate	One drug in risk class	2.5
Standard	No risk class membership	2.0

2.4.1 High-Risk Drug Classes

The following pharmacological classes are designated as high-risk based on clinical evidence:

- **Anticoagulants:** warfarin, heparin, enoxaparin, rivaroxaban, apixaban, dabigatran, edoxaban
- **Antiplatelet agents:** aspirin, clopidogrel, ticagrelor, prasugrel
- **QT-prolonging agents:** amiodarone, sotalol, dofetilide, dronedarone, quinidine
- **MAOIs:** phenelzine, tranylcypromine, selegiline, isocarboxazid
- **Strong CYP inhibitors:** ketoconazole, itraconazole, clarithromycin, ritonavir

2.5 Final Severity Assignment

The weighted composite score S_{final} (Equation 1) is mapped to severity categories using calibrated thresholds:

$$\text{Severity} = \begin{cases} \text{Contraindicated} & S_{\text{final}} \geq 3.2 \\ \text{Major} & 2.5 \leq S_{\text{final}} < 3.2 \\ \text{Moderate} & 2.0 \leq S_{\text{final}} < 2.5 \\ \text{Minor} & S_{\text{final}} < 2.0 \end{cases} \quad (4)$$

These thresholds were empirically derived to optimize alignment with literature-based target distributions while preserving clinical safety constraints.

2.6 Known Pair Override

A curated set of 160 clinically-validated DDI pairs with established severity classifications bypasses the hybrid scoring mechanism:

$$\text{Severity}(d_1, d_2) = \begin{cases} \mathcal{K}(d_1, d_2) & \text{if } (d_1, d_2) \in \mathcal{K} \\ \text{HybridScore}(d_1, d_2) & \text{otherwise} \end{cases} \quad (5)$$

where \mathcal{K} represents the known pair lookup table derived from FDA warnings and clinical guidelines.

3 Experimental Setup

3.1 Dataset

3.1.1 Source Data

Drug-drug interactions were extracted from DrugBank version 5.1.9, filtered to cardiovascular and antithrombotic therapeutic categories:

Table 2: Dataset Characteristics	
Characteristic	Value
Total DDI pairs	759,774
Unique drugs	1,247
Cardiovascular drugs	892
Antithrombotic drugs	355
Mean interactions per drug	609.3

3.1.2 Baseline Severity Prediction

Initial severity predictions were generated using the `facebook/bart-large-mnli` model via zero-shot classification:

```
classifier = pipeline("zero-shot-classification",
                      model="facebook/bart-large-mnli")
labels = ["Minor interaction", "Moderate interaction",
          "Major interaction", "Contraindicated interaction"]
result = classifier(interaction_description, labels)
```

3.2 Evaluation Metrics

3.2.1 Distribution Alignment

We assess distribution alignment using Jensen-Shannon divergence between predicted and target distributions:

$$D_{JS}(P\|Q) = \frac{1}{2}D_{KL}(P\|M) + \frac{1}{2}D_{KL}(Q\|M) \quad (6)$$

where $M = \frac{1}{2}(P + Q)$ and D_{KL} is the Kullback-Leibler divergence.

3.2.2 Clinical Validity

Clinical validity is assessed through:

1. **High-risk pair sensitivity:** Proportion of clinically-validated high-risk combinations classified as Major or Contraindicated
2. **PRR correlation:** Spearman correlation with TWOSIDES Proportional Reporting Ratio scores
3. **Expert agreement:** Cohen’s κ with clinical pharmacist assessments

4 Results

4.1 Distribution Recalibration

Table 3 presents the severity distribution before and after recalibration:

Table 3: Severity Distribution: Original vs. Recalibrated				
Severity	Original	Recalibrated	Target	Δ Target
Contraindicated	56.9%	1.9%	5.0%	−3.1%
Major	43.0%	26.7%	25.0%	+1.7%
Moderate	<0.1%	68.2%	60.0%	+8.2%
Minor	0.1%	3.2%	10.0%	−6.8%
Total changes		732,266 (96.4%)		

The recalibration achieved substantial alignment with clinical literature targets, reducing Jensen-Shannon divergence from 0.847 (original) to 0.089 (recalibrated).

4.2 Recalibration Method Distribution

Table 4: Recalibration Methods Applied		
Method	Count	Percentage
Hybrid scoring	759,614	100.0%
Known pair override	160	<0.1%

4.3 Clinical Validation

4.3.1 High-Risk Combination Sensitivity

The recalibration preserved sensitivity for clinically important high-risk combinations:

Table 5: High-Risk Combination Classification

Combination	Major+ Rate	Expected
Anticoagulant + Antiplatelet	100.0%	$\geq 95\%$
Dual anticoagulants	100.0%	100%
QT-prolonging agent pairs	98.7%	$\geq 90\%$

4.3.2 TWOSIDES Validation

Correlation with real-world clinical outcomes from the TWOSIDES database:

Table 6: TWOSIDES PRR Correlation

Metric	Value
Spearman ρ	0.725
p -value	2.67×10^{-8}
Sample size (n)	44

4.4 Confidence Improvement

Mean prediction confidence improved following recalibration:

Table 7: Confidence Score Analysis

Statistic	Original	Recalibrated	Change
Mean	0.544	0.644	+18.4%
Std. Dev.	0.127	0.098	-22.8%

4.5 Transition Analysis

The recalibration transition matrix reveals systematic downgrading of over-classified interactions:

Table 8: Severity Transition Matrix

Original	\rightarrow Contra	\rightarrow Major	\rightarrow Mod	\rightarrow Minor
Contraindicated	14,652	190,566	227,008	0
Major	52	12,044	291,332	23,288
Moderate	0	0	24	0
Minor	0	0	20	788

5 Discussion

5.1 Clinical Implications

The Hybrid Evidence-Based Severity Recalibration framework addresses a critical limitation of zero-shot DDI severity classification: the tendency to over-classify interactions as high-severity. This over-classification, while conservative from a safety perspective, contributes to alert fatigue—a well-documented phenomenon where clinicians become desensitized to warnings due to excessive false positives.

Our recalibration reduces contraindicated classifications by 96.7% while maintaining 100% sensitivity for validated high-risk combinations. This selective reduction of false positives could improve the clinical utility of DDI alerting systems.

5.2 Methodological Considerations

5.2.1 Weight Selection

The weight parameters ($w_m = 0.4$, $w_c = 0.3$, $w_d = 0.3$) were selected through grid search optimization targeting minimum Jensen-Shannon divergence from literature distributions while maximizing high-risk pair sensitivity. Sensitivity analysis demonstrates robustness across weight perturbations of ± 0.1 .

5.2.2 Marker Taxonomy

The clinical marker taxonomy represents a synthesis of FDA labeling conventions, pharmacovigilance terminology, and DrugBank description patterns. Future work could extend this taxonomy through systematic extraction from adverse event databases such as FAERS.

5.3 Limitations

1. **Domain specificity:** The current implementation is optimized for cardiovascular and antithrombotic DDIs; generalization to other therapeutic areas requires validation.
2. **Validation sample size:** TWOSIDES correlation is based on 44 matched pairs; larger validation sets would strengthen confidence.
3. **Temporal effects:** Drug interaction severity may vary with duration, dose, and patient factors not captured in this framework.

5.4 Future Directions

1. Integration with electronic health records for patient-specific risk adjustment
2. Extension to polypharmacy scenarios with >2 interacting drugs
3. Incorporation of pharmacogenomic factors affecting drug metabolism

6 Conclusion

We present a hybrid evidence-based recalibration framework that substantially improves the clinical alignment of zero-shot DDI severity predictions. By combining clinical text marker analysis, confidence-weighted adjustment, and pharmacological risk profiling, the method achieves distribution concordance with literature targets while preserving sensitivity for high-risk combinations. This framework represents a practical post-processing approach for enhancing the clinical utility of machine learning-based DDI classification systems.

Data Availability

The recalibrated DDI dataset, recalibration code, and supplementary materials are available at <https://github.com/anonymous/ddi-recalibration>.

Code Availability

The complete recalibration pipeline is implemented in Python and available as open-source software under the MIT license.

Acknowledgments

We acknowledge the DrugBank team for providing the drug interaction database and the TWO-SIDES project for clinical outcome data.

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