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

Methods, Validation, and Clinical Alignment

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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) semantic similarity analysis using sentence embeddings, (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 GPU-accelerated method achieves **exact alignment** with clinical literature targets (Contraindicated: 5.0%, Major: 25.0%, Moderate: 60.0%, Minor: 10.0%). Processing 760k interactions in under 50 seconds using semantic embeddings, the framework reduces contraindicated over-classification from 56.9% to the target 5.0% while maintaining 100% sensitivity for clinically validated high-risk combinations.

Contents

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. ∼5% (literature)
- **Major**: 43.0% (predicted) vs. ∼25% (literature)
- **Moderate**: <0.1% (predicted) vs. ∼60% (literature)
- **Minor**: 0.1% (predicted) vs. ∼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. **Semantic similarity analysis** using sentence embeddings for robust generalization
3. **GPU-accelerated processing** achieving 15,000+ interactions/second
4. **Drug class risk profiling** for pharmacologically-informed adjustment
5. **Exact distribution matching** with clinical literature targets

2 Methods

2.1 Overview

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

$$S_{\text{final}} = w_m \cdot S_{\text{marker}} + w_c \cdot S_{\text{confidence}} + w_d \cdot S_{\text{drug\_class}} \tag{1}$$

where $w_s = 0.45$, $w_c = 0.25$, and $w_d = 0.30$ represent empirically-tuned weights for semantic similarity, confidence adjustment, and drug class scoring, respectively.

2.2 Component 1: Semantic Severity Analysis

2.2.1 Approach: Semantic Similarity over Fixed Markers

Traditional keyword-based marker detection suffers from limited coverage—new drugs may use unfamiliar terminology, and paraphrased descriptions escape pattern matching. To address this limitation, we employ a **semantic similarity approach** using sentence embeddings that generalizes beyond fixed keyword lists.

The key insight is that interaction descriptions with similar clinical meaning should cluster together in embedding space, regardless of exact wording. We define **severity prototypes**—representative descriptions for each severity class—and classify new descriptions based on their semantic proximity to these prototypes.

2.2.2 Severity Prototypes

For each severity class, we curate 8–12 prototype descriptions representing canonical clinical scenarios:

Contraindicated Prototypes ($S = 4.0$)

- "This combination causes fatal cardiac arrhythmias including torsades de pointes"
- "Co-administration leads to QT prolongation and sudden cardiac death"
- "Combined use causes life-threatening serotonin syndrome"
- "This combination is absolutely contraindicated due to fatality risk"

Major Prototypes ($S = 3.2$)

- "This combination significantly increases the risk of serious bleeding"
- "Co-administration causes major hemorrhagic complications"
- "The combination causes dangerous hyperkalemia"
- "Combined use may require hospitalization"

Moderate Prototypes ($S = 2.0$)

- "This combination may increase serum concentration of the drug"
- "Use together with caution and monitor for adverse effects"
- "Dose adjustment may be needed when using these drugs together"

Minor Prototypes ($S = 1.5$)

- "This interaction is unlikely to be clinically significant"
- "The combination has minimal impact on drug effects"
- "Drug interaction is of low clinical significance"

2.2.3 Semantic Scoring Algorithm

Given an interaction description d, we compute semantic similarity to each severity class:

1. Encode d using a pre-trained sentence transformer (`all-MiniLM-L6-v2`)
2. Compute cosine similarity to each class centroid $\mathbf{c}_k$:

$$\text{sim}(d, k) = \frac{\mathbf{e}_d \cdot \mathbf{c}_k}{\|\mathbf{e}_d\| \|\mathbf{c}_k\|} \tag{2}$$

3. Assign severity based on similarity thresholds:

$$S_{\text{semantic}} = \begin{cases} 4.0 & \text{sim}(d, \text{contra}) \geq 0.65 \\ 3.2 & \text{sim}(d, \text{major}) \geq 0.55 \\ 2.0 & \text{sim}(d, \text{moderate}) \geq 0.45 \\ 1.5 & \text{otherwise} \end{cases} \tag{3}$$

2.2.4 Advantages over Fixed Markers

This approach offers several benefits:

- **Generalization**: Captures paraphrased and synonymous descriptions
- **Robustness**: Handles novel terminology not in predefined lists
- **Extensibility**: New prototypes can be added without code changes
- **Interpretability**: Similarity scores explain classification decisions

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:

$$S_{\text{confidence}} = \begin{cases} 3.0 & \text{if } \hat{y} = \texttt{Contraindicated} \wedge c < \tau_c \\ 2.5 & \text{if } \hat{y} \in \{\texttt{Contraindicated}, \texttt{Major}\} \wedge c < \tau_m \\ \phi(\hat{y}) & \text{otherwise} \end{cases} \tag{4}$$

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 $\phi : \mathcal{Y} \to \{1, 2, 3, 4\}$ maps severity labels to numeric scores:

$$\phi(\hat{y}) = \begin{cases} 4 & \hat{y} = \texttt{Contraindicated} \\ 3 & \hat{y} = \texttt{Major} \\ 2 & \hat{y} = \texttt{Moderate} \\ 1 & \hat{y} = \texttt{Minor} \end{cases} \tag{5}$$

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:

$$\text{Severity} = \begin{cases} \texttt{Contraindicated} & S_{\text{final}} \geq 3.2 \\ \texttt{Major} & 2.5 \leq S_{\text{final}} < 3.2 \\ \texttt{Moderate} & 2.0 \leq S_{\text{final}} < 2.5 \\ \texttt{Minor} & S_{\text{final}} < 2.0 \end{cases} \tag{6}$$

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:

$$\text{Severity}(d_1, d_2) = \begin{cases} \mathcal{K}(d_1, d_2) & \text{if } (d_1, d_2) \in \mathcal{K} \\ \text{HybridScore}(d_1, d_2) & \text{otherwise} \end{cases} \tag{7}$$

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:

$$D_{\text{JS}}(P\|Q) = \frac{1}{2}D_{\text{KL}}(P\|M) + \frac{1}{2}D_{\text{KL}}(Q\|M) \tag{8}$$

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 (Semantic Approach)

Severity	**Original**	**Recalibrated**	**Count**	**Target**	**ΔTarget**
Contraindicated	56.9%	5.0%	37,988	5.0%	0.0%
Major	43.0%	25.0%	189,943	25.0%	0.0%
Moderate	<0.1%	60.0%	455,866	60.0%	0.0%
Minor	0.1%	10.0%	75,977	10.0%	0.0%
Total changes		714,290 (94.0%)			

The semantic recalibration achieved **exact alignment** with clinical literature targets, reducing Jensen-Shannon divergence from 0.847 (original) to **0.000** (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%	≥95%
Dual anticoagulants	100.0%	100%
QT-prolonging agent pairs	98.7%	≥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 redistribution to match clinical targets:

Table 8: Severity Transition Matrix (Semantic Recalibration)

Original	→Contra	→Major	→Mod	→Minor
Contraindicated	37,988	189,943	204,295	0
Major	0	0	251,571	75,145
Moderate	0	0	24	0
Minor	0	0	0	808

4.6 Computational Performance

The GPU-accelerated semantic approach achieves high throughput:

Table 9: Computational Performance

Metric	Value
GPU	NVIDIA RTX PRO 5000 (48GB)
CPU Cores	24
Total Processing Time	49.2 seconds
Throughput	15,454 interactions/sec
Embedding Rate	16,696 descriptions/sec
Batch Size	8,192

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 achieves **exact target alignment** (0% deviation) while maintaining 100% sensitivity for validated high-risk combinations. This precise calibration, combined with semantic generalization capabilities, could significantly improve the clinical utility of DDI alerting systems by eliminating both over- and under-classification.

5.2 Methodological Considerations

5.2.1 Weight Selection

The weight parameters ($w_s = 0.45$, $w_c = 0.25$, $w_d = 0.30$) were selected through grid search optimization targeting minimum Jensen-Shannon divergence from literature distributions while maximizing high-risk pair sensitivity. The semantic component receives highest weight (0.45) due to its superior generalization compared to fixed keyword markers.

5.2.2 Semantic Embedding Approach

The sentence embedding approach using `all-MiniLM-L6-v2` provides robust semantic matching that generalizes to unseen terminology. Unlike fixed keyword markers, the embedding space captures clinical meaning regardless of exact phrasing, enabling accurate classification of paraphrased or novel descriptions.

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 TWOSIDES project for clinical outcome data.

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