# An Automated System for Detecting Adverse Drug-Drug Interactions Associated with Hypotension in a Critical Care Setting

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**Abstract**

*Adverse drug-drug interactions (DDIs) raise great concern in the medical intervention process especially in the critical care setting because many critical care patients require polypharmacy to effectively manage their illnesses whereas the sensitive population is particularly vulnerable to adverse DDI events. Even though DDIs continue to be one of the most preventable critical care complications, many escape unnoticed due to the complexity in systemically detecting signals. In this study, an automated system was devised and developed for clinicians to identify drug combinations that potentially lead to adverse events associated with DDIs. The application of our system is restricted to detecting signals associated with hypotensive events but can be easily extended to any possible adverse event in future studies. The system returns potential DDI factor scores based on disproportionality analysis of the MIMIC-III database. Validating disproportionality analysis with both association rule mining and omega shrinkage measures, the system identifies potential DDIs associated with hypotensive events.*

**Introduction**

Over 30% of the unexpected adverse drug events is attributable to drug-drug interactions (DDIs) because it is taxing and even unrealistic to carry out comprehensive clinical trials to detect all potential DDIs and manually review all the signals.[1] Despite systemic and institutional efforts taken to reduce drug interaction risk, DDIs and associated adverse events remain prevalent and uncharted.[2] Therefore, development of data-driven methods that can detect DDIs with low human resource costs are critical to facilitate physician decision making and improve healthcare outcomes. Furthermore, DDIs constitute a greater concern in the critical care setting due to the nature of critical care patients and the intensity of medical intervention involved. Clinical management of critically ill patients almost always involves the administration of multiple drugs, thus sharply increasing the risk of adverse health outcomes due to DDIs.[2] Physicians in the ICU setting have an intense and complicated workflow, which makes risk-stratifying potential drug interactions a cumbersome additional task. Although data on adverse drug interaction events is available, this information is not always easily accessible and processible in time-sensitive scenarios. This further suggests the need for an automated system in the ICU clinical decision making toolkit that can screen for potential drug interactions both accurately and efficiently.

Identification and validation of potential DDIs have always been an active area of research. Previous work to risk-stratify DDIs has relied on detailed evaluation of molecular targets, but resorting to EHR data-mining algorithms (DMAs) or signal detection algorithms has recently been established as promising strategy for identifying DDIs due to the efficiency.[1,5] Some work employed data mining algorithms such as the association rule mining to find prevalent combinations of drugs and the adverse event, and then filtered the result by computing relative reporting ratio to obtain a list of potential associations between DDI and resulting adverse events.[5] Some utilized propensity score matching to address the prescribing bias and estimate the odds ratio of having adverse events after prescribing certain drug combination.[6] Others also have adopted NLP methods to preprocess discharge summaries and then used machine learning-based techniques such as deep learning to perform named entity recognition and relation classification to identify adverse drug events.[7] The majority of the work focused on analyzing structured data from spontaneous reporting systems such as the adverse event reporting systems (AERSs), or unstructured data from EHR databases, whereas our study focused on the structured data from the EHR database, MIMIC-III, and characterized the adverse events potentially associated with DDIs that can be extrapolated from charted laboratory data.

To be more specific, our study seeks to develop an automated system that processes structured lab data and identifies drug pairings associated with hypotensive events. Hypotension is a potential DDI-related adverse event that is associated with decompensation, organ failure, and death.[3,4] Additionally, since vital signs are monitored constantly

on every patient in the ICU, it is virtually impossible for a hypotensive event to go unrecorded, reducing the chance of indication bias or reporting bias in our results.

**Methods**

Since the method and result sections are tailored to my specific contributions in this study, I will only cover the portion of data ingestion and disproportionality analysis.

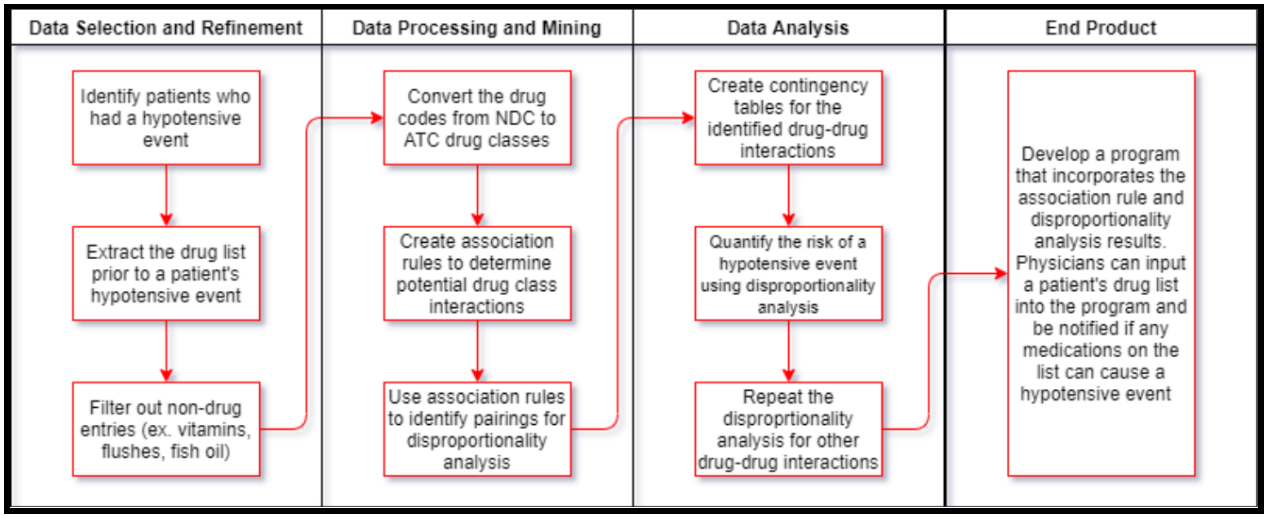


**Figure 1.** Study Overview

Flags of hypotensive reading and the corresponding prescriptions prior to the reading were extracted from the "CHARTEVENTS" and "PRESCRIPTIONS" table from the MIMIC-III critical care database. Then the drugs will be assigned with ATC4 classification groups in order to reduce the dimensionality of the data. We then performed disproportionality analysis to identify the drug combinations with high observed-to-expected rate of hypotensive outcomes, and validated the results based on the calculated statistical shrinkage measures. Ultimately, we developed a program incorporating the estimated risk of hypotension associated with different pairwise drug combinations, and users are able to input an ATC4 code combination and receive corresponding risk consideration for them. The end product along with all the processing and analyses performed were in the Julia programming language (v.1.5.3).

*MIMIC-III Database*

The data comes from the MIMIC-III database, an openly available database of de-identified and comprehensive health record data of over 60,000 ICU admissions at Beth Israel Deaconess Medical Center between 2001 and 2012.[8] The database contains both structured and unstructured data on patient demographics, vital signs, laboratory test results, mortality, inpatient procedures, prescriptions, imaging reports, etc.[9] Our study utilized the structured data from the "CHARTEVENTS" and "PRESCRIPTIONS" table. We extracted the lists of prescriptions from patients who have had a hypotensive event (defined as a systolic blood pressure value < 90). The prescription lists only contain drugs administered up to 48 hours prior to the hypotensive reading. Drugs with drug type of "BASE" and drugs with null "DRUG_NAME_GENERIC" values were all removed because they are non-drug entries. One complication here that potentially induces bias to our results is that the prescription table does not have timestamps specific to hours and minutes, thus the exact length of time between drug administration and a hypotensive event is unknown and can range anywhere from -24 hours to 47 hours. Also there exists edge cases where two drugs were prescribed at the end of day one and the start of day two but were not included as concomitant using drugs, which can also result in bias in our results.

*ATC classification*

The prescriptions in the MIMIC-III database have corresponding National Drug Code (NDC) codes on record. We mapped the NDC codes onto Anatomical Therapeutic Chemical (ATC) Classification System codes in order to reduce the dimensionality of the prescription data. ATC classification codes include 5 levels of specificity ranging from the broadest anatomical or pharmacological level to the most specific chemical substance level. We mapped

our NDCs to the fourth ATC classification level, which is the broader chemical level, so that the biochemical nature of drug interactions with the enzymes/proteins can be mainly preserved while the dimensionality of the data can be reduced simultaneously. In the mapping process, we restricted the ATC4 grouping assignment to one per drug even though some drugs can be classified into multiple classes in order to maintain the intention of dimensionality reduction. To do so, we prioritized the assignment of cardiovascular class if multiple assignments were possible, because medications treating cardiovascular diseases have higher potential in resulting in adverse DDI events.[10] Patients taking cardiovascular drugs have are anticipated to have cardiovascular-related conditions, while patients with cardiovascular diseases (CVDs) are known to be susceptible to adverse DDI events due to the fact that CVDs impair the mechanism of drug metabolism.[10] Therefore, when mapping the drug codes, we prioritized the grouping of the cardiovascular drugs.

*Disproportionality Analysis*

To generate hypotheses of potential DDI associated with the hypotension, we performed disproportionality analysis to calculate the observed-to-expected ratio of hypotensive events resulting from concomitant drug use. The concrete methodology of the disproportionality analysis was adopted from Norén et al's statistical model.[11]

The observed-to-expected ratio used to determine the disproportionality of the adverse events is characterized as:

$$OR = \frac{f_{11}}{E[f_{11}]}$$

which is the ratio of observed relative reporting ratio (RRR) of the hypotensive event given the concomitant use of two drugs, and the expected RRR calculated from respective RRRs given the prescription of one drug and not the other.

**Table 1.** Contingency table for disproportionality analysis, counting frequencies

| | Drug exposure to both drugs | Drug exposure to neither drugs | Drug exposure to drug1 but not drug2 | Drug exposure to drug2 but not drug1 |
|---|---|---|---|---|
| Hypotensive events occured | $n_{111}$ | $n_{001}$ | $n_{101}$ | $n_{011}$ |
| Number of reports in total | $n_{11-}$ | $n_{00-}$ | $n_{10-}$ | $n_{01-}$ |

**Table 2.** Calculation of respective observed relative reporting ratios

| | Drug exposure to both drugs | Drug exposure to neither drugs | Drug exposure to drug1 but not drug2 | Drug exposure to drug2 but not drug1 |
|---|---|---|---|---|
| Observed RRR | $f_{11} = \frac{n_{111}}{n_{11-}}$ | $f_{00} = \frac{n_{001}}{n_{00-}}$ | $f_{10} = \frac{n_{101}}{n_{10-}}$ | $f_{01} = \frac{n_{011}}{n_{01-}}$ |

In the disproportionality analysis, we first recorded the frequencies of hypotensive events under different prescription conditions as shown in table 1. When counting the frequencies with different prescription conditions across all prescriptions, one "report" of prescription is defined as at least one prescription within a stamped day, meaning that multiple prescriptions of the same drug were counted as one occurence. Then we can use the frequencies to calculate the observed RRR as shown in table 2.

To estimate the expected RRR, we had to make a few important assumptions to set up the statistical framework: 1) The risk of hypotension is attributable to background factors such as the underlying disease or a random event, thus the risk of hypotension with exposure to neither drugs is simply the background risk. 2) The co-prescribed drugs do

not interact, meaning that the attributable risks to each drug are independent. 3) The background risk is estimable. The expected RRR then can be derived from the attributable risks, and eventually takes the form of:

$$E(f_{11}) = 1 - \frac{1}{\frac{f_{10}}{1-f_{10}} + \frac{f_{01}}{1-f_{01}} - \frac{f_{00}}{1-f_{00}} + 1}$$

Nonetheless, the estimated attributable risks can take negative values and bias our results. Therefore, in order to offset such potential risks, we revised the equation and replace attributable risks with the background risk if attributable risks are smaller than background risk (indicating biased-estimation of the attributable risks):

$$E(f_{11}) = 1 - \frac{1}{max(\frac{f_{00}}{1-f_{00}}, \frac{f_{10}}{1-f_{10}}) + max(\frac{f_{00}}{1-f_{00}}, \frac{f_{01}}{1-f_{01}}) - \frac{f_{00}}{1-f_{00}} + 1}$$

*Omega Shrinkage Measure*

Calculating the observed-to-expected ratio alone is not a robust method to estimate the disproportionality because the estimated ORs can have very high variance when sample size of the observed adverse events is small or the expected numbers of events are small, and the results are particularly unstable when the expected frequency is lower than one.[12] Therefore, a statistical shrinkage method was adopted to help evaluate the results obtained from the disproportionality analysis. The intuition for this method is that it protects against the spurious associations by shrinking the estimates towards zero if the data is insufficient in determining disproportionality.[12] The shrinkage measure is calculated as:

$$\Omega_0 = log_2 \frac{f_{11}}{g_{11}} = log_2 \frac{\frac{n_{111}}{n_{11}}}{g_{11}} = log_2 \frac{n_{111}}{g_{11} \cdot n_{11}}$$

Therefore:

$$\Omega = log_2 \frac{n_{111} + \alpha}{g_{11} \cdot n_{11} + \alpha}$$

where alpha is a shrinkage parameter that determines how much the measure of disproportionality will shrink towards 0. In our study, we set the parameter to 0.5 in all the analyses, in accordance with the literature that suggests the magnitude of 0.5 provides enough shrinkage without losing potentially important information.[11]

**Results**

Disproportionality analysis with shrinkage measures were applied to the data with 1,954,051 prescription entries in ATC4. The list of drugs prescribed prior to the hypotensive event contain 121,436 entries, with the subgroup of prescriptions of each patient having unique drug entries. In total, there are 16,565 unique pairwise drug combinations analyzed.

**Table 3.** Drug combinations with top 5 omega shrinkage measures

| Drug 1 | Drug 2 | OR | Omega |
|---|---|---|---|
| Anticholinesterases | Sulfonamides | 35.6 | 5.1 |
| Anticholinesterases | Opioids | 13.8 | 3.8 |
| Anticholinesterases | Glycogenolytic hormones | 13.0 | 3.7 |
| Anticholinesterases | ACE inhibitors | 12.3 | 3.6 |
| Sulfonamides | Opioids | 11.4 | 3.5 |

**Table 4.** Drug combinations (with at least one cardiovascular class drug) with top 5 omega shrinkage measures

| Cardiovascular drug 1 | drug 2 | OR | Omega |
|---|---|---|---|
| Sulfonamides | Anticholinesterases | 35.6 | 5.1 |
| ACE inhibitors | Anticholinesterases | 12.3 | 3.6 |
| Sulfonamides | Opioids | 11.4 | 3.5 |
| Beta blocking agents | Anticholinesterases | 8.1 | 3.0 |
| Nitroferricyanide derivatives | Opioids | 9.9 | 2.6 |

The estimated observed-to-expected ratios and the omega shrinkage measures with highest values are summarized in the table 3. The table 4 contains the highest shrinkage estimates of drug combinations with at least one drug treating cardiovascular conditions. The results omit combinations including at least one type of laxatives, antihydrotics, or diuretics because they are commonly administered drugs in the critical care setting.

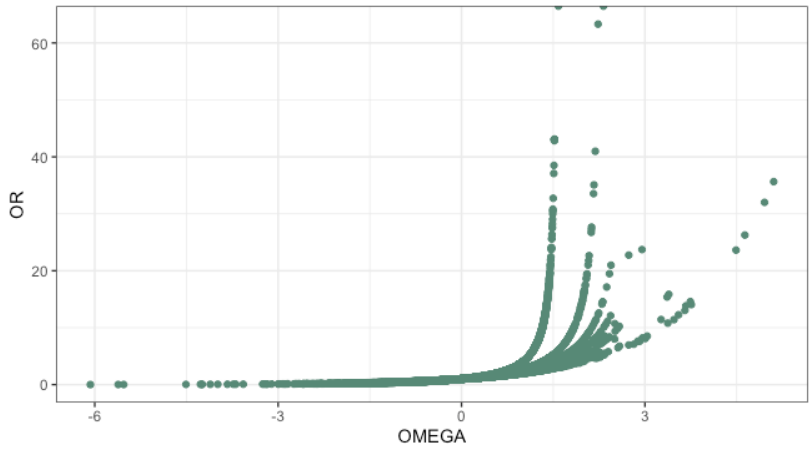


**Figure 2.** Association of OR and OMEGA values of all the drug pairs

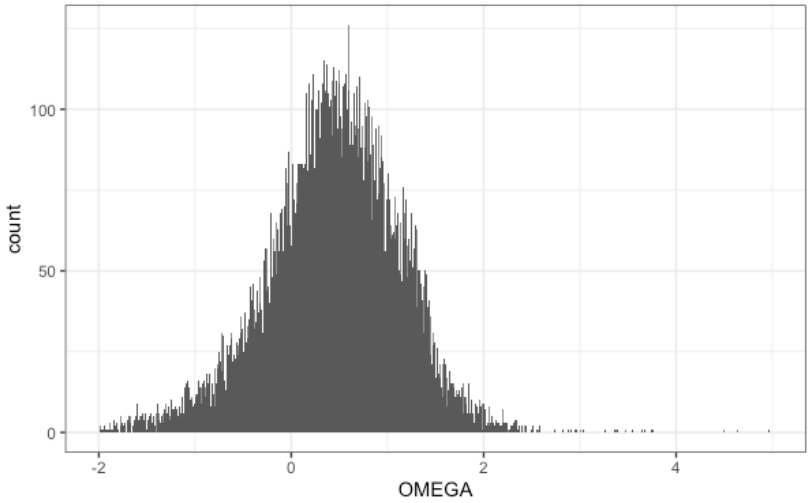


**Figure 3.** Distribution of Omega shrinkage measures, bell-shaped, mean over 0

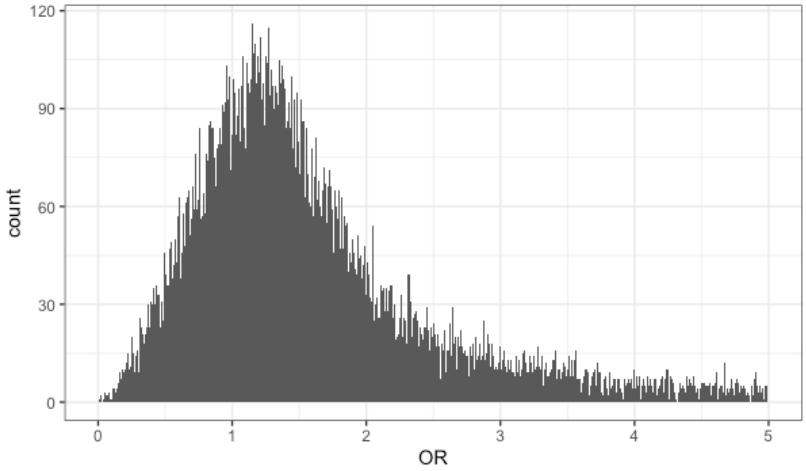


**Figure 4.** Distribution of OR, skewed to the right, mean over 1

Figure 2 suggests that the magnitude of shrinkage depends on the observed and expected frequencies of adverse events. Drug pairs with high observed-to-expected ratios can be shrinked towards null value. Figure 3 shows that the distribution of the omega shrinkage measures is bell-shaped, and the mean is over 0, meaning that over half of the pairwise drug combinations were flagged to have signals of potential DDI associated with hypotension. The results from the observed-to-expected ratios are also consistent with those from the shrinkage measures: over half of the drug pairs have ORs higher than 1, which indicates deviation.

**Discussion**

The shrinkage measure adopted in our study, adapted from Norén et al.'s study, is equipped with better interpretability as compared to other commonly used shrinkage methods such as the Information Criterion (IC) or the Multi-Item Gamma Poisson Shrinker (MGPS) because of its simplicity and transparency in the setup.[11] Interpretability is crucial to our study because we need a measure that is easily conveyable to medical practitioners without statistical backgrounds. The results from the analyses show that, for instance, the observed hypotensive events given the concomitant use of anticholinesterases and sulfonamides are at least 5.1 times as many as what was expected to be the frequency of hypotensive events, based on each drug's separate risk profile. However, the shrinkage measure should not be reported without also reporting observed-to-expected ratios because the magnitude

of the shrinkage depends totally on the choice of the shrinkage parameter, so the shrinkages need to be complemented with other measures to give an overview of the associated risks.

In our results, more than half of the drug pairs have shrinkage estimates larger than 0, thus they are all labeled as pairs with potential DDI associated with hypotension. The unexpectedly large number of signals detected is due to the many limitations in our study design. First of all, this could potentially be a consequence of the violation of the underlying assumption for our method. When estimating the expected relative reporting rates given co-prescription of the drug pair, it's assumed that there's a background risk due to underlying disease or other chance events and this background risk can be estimated with our model. However, if other drugs have large attributable risks for hypotension, or other underlying disease conditions have large attributable risks, our estimate for the background risk will be too high and consequently the observed-to-expected ratio/shrinkage measures will be overestimated. To address this potential problem, as suggested by literature, we can modify the omega measure with the new assumption that there's no background risk of hypotension.[11] The assumption is more extreme but can help determine if false positive results will be substantially reduced. Furthermore, future studies should construct confidence intervals for the omega shrinkage estimates and compare the lower limit of the confidence interval to 0 as the criteria of flagging potential DDIs.

The grouping of the drugs on the fourth ATC level can also potentially lead to biased results. More research on the suitability of ATC codes in DDI analyses should be conducted, validating established DDIs on the ATC4 level against the values obtained from such disproportionality analysis. Another direction we should take in the future is to refine the data extraction program for a more rigorous data ingestion procedure. We used structured clinical data instead of data from self reporting systems that can be separated into cases of reports. Therefore, the frequency of events in the disproportionality analysis in our study heavily depends on what we define as one occurrence of adverse events and what we define as concomitant use of drugs.

**Conclusion**

We were able to use disproportionality analysis accompanied by omega shrinkage measures to conduct a fairly reasonable study of drug interactions associated with hypotension. Nevertheless, there is scope for improvement in this system. Currently, our mapping of ATC codes still includes non-drug entries and frequently used drugs, which should be removed for better results. Additionally, the significance of our results is based on the choice of shrinkage parameter of 0.5 for the omega shrinkage measurement. Upon observation, the drug pairs with DDIs associated with hypotension are in accordance with our anticipation, including drugs like cardiac stims and antiarrhythmics that are linked with hypertension, because our statistical models do not adjust for confounding effects well enough, but these are potentially promising results that we can remove by further refining our program.

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