Identifying Drug Interaction Effects on Myopathy at the ATC Group Level

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1. Background

- Mining high-order drug-drug interaction (DDI) induced adverse drug effects (ADEs) from electronic health record (EHR) databases is an emerging area, and very few studies have explored the relationships between DDIs.
- We previously studied a novel pharmacovigilance problem for mining directional drug interaction effect on myopathy [1] using the FDA Adverse Event Reporting System (FAERS) database.
- Given over 1,500 FDA approved drugs, the number of candidate directional ADE effects between two drug combinations could be prohibitively huge, and many of these drug combinations have zero or very few occurrences in the data.
- Since different drugs could share similar pharmacological and other properties, grouping similar drugs together and performing group-level analysis instead of drug-level analysis could dramatically reduce the problem dimensionality, boost the drug-group combination occurrences in the data, and yield high-level and interpretable results.
- Therefore, in this work, we propose to perform high order directional ADE effect analysis at the group level, using the Anatomical Therapeutic Chemical (ATC) classification system.

2. Methods

- We employed the 3rd-level ATC codes to define drug groups using their shared therapeutic properties. Each drug group was re-annotated as a new drug, and its interaction with other drugs and/or drug groups was treated just like individual drugs.
- The analysis was applied to the FAERS data (between Q4 2012 and Q2 2015), which were de-duplicated and standardized using the AEOLUS pipeline [2]. Using the frequent itemset mining FP-Growth implementation, we analyzed frequent ATC combinations in FAERS.
- As shown in **Figure 1**, we estimated the odds ratio (OR) of the directional myopathy risk from taking $ATCC_1$ to taking $ATCC_1$ U $ATCC_2$, where both $ATCC_1$ and $ATCC_2$ are frequent.

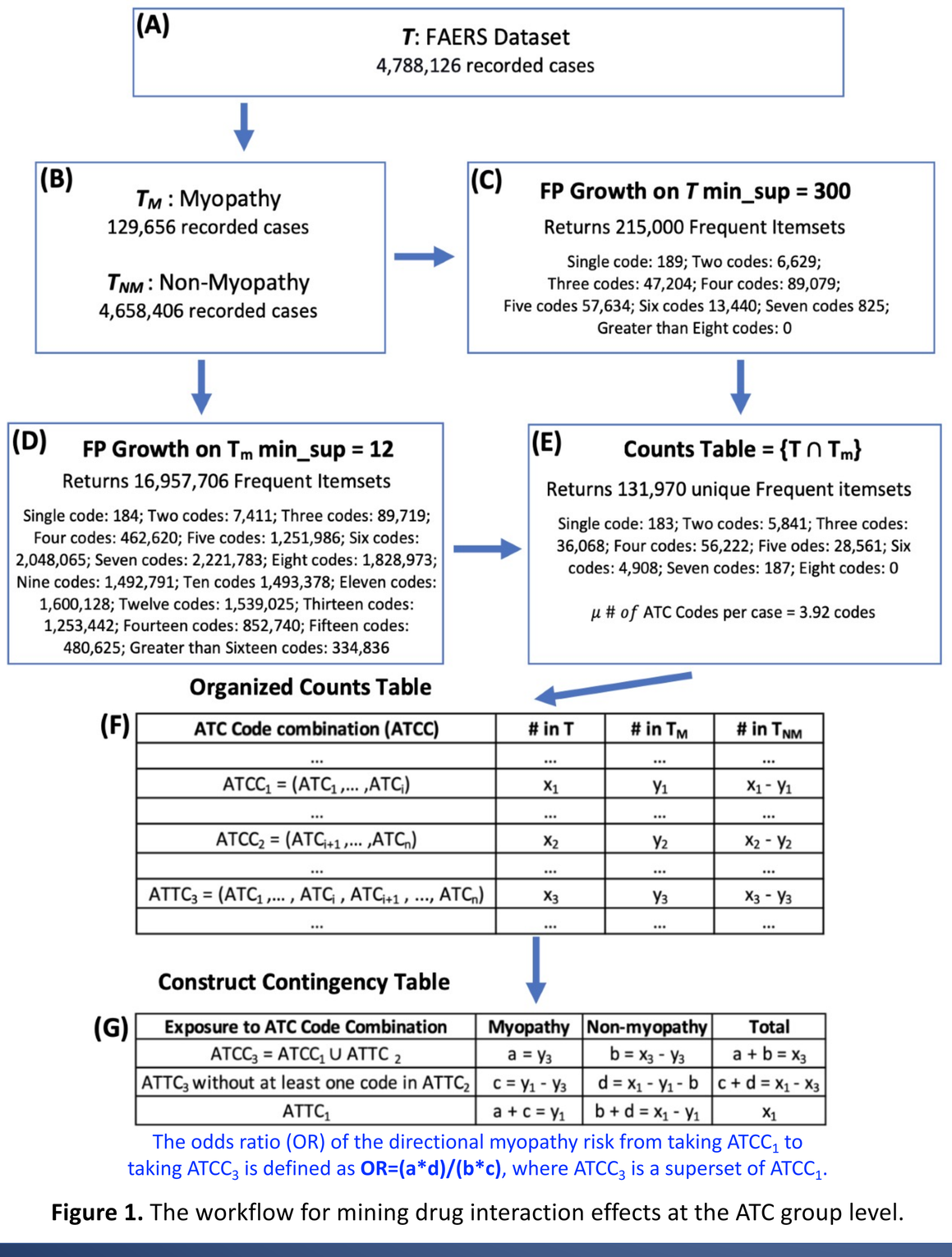

Figure 1. The workflow for mining drug interaction effects at the ATC group level.

3. Results

- Selected combinations of antecedent and consequents for ATC code combinations were analyzed and top odds ratio findings were reported (**Table 1** and **Table 2**).
- The combination of the ATC codes most present in the odds ratio top findings are shown in **Table 1**. The top finding S01H, S01A --> S01H, S01A, A02B is a two ATC code combination of local anesthetics and combinations with antibiotics which when a drug in the A02B group representing drugs for Peptic Ulcer and Gastro Osteophageal Reflux disease is added produces a drug-drug interaction that leads to a substantial increase in the risk of myopathy odds ratio = 43.093. This means that the myopathy risk for patients taking the combination of local anesthetics, combinations with antibiotics, and Peptic Ulcer and Gastro Osteophageal Reflux disease is 43.093 times higher than that for patients taking only local anesthetics and combinations with antibiotics.

Table 1: OR Top 15 Findings All ATC Combinations

Rank	ATC Code Antecedent	ATC Code Consequent	Odds Ratio
1	S01H,S01A	S01H,S01A,A02B	43.093
2	J01A,J01R,R03A	J01A,J01R,R03A,A02B	20.791
3	V03A,C03E,R03A,N06A	V03A,C03E,R03A,N06A,A02B	20.295
4	R05C,J01M,R03A	R05C,J01M,R03A,A02B	20.062
5	R03B,N05A,C09B,N03A	R03B,N05A,C09B,N03A,A02B	19.931
6	R03D,N05C,N05A,N03A	R03D,N05C,N05A,N03A,A02B	19.907
7	G04B,C03E,N05C,C09B	G04B,C03E,N05C,C09B,A02B	19.898
8	A04A,C07F,N05B,C09B	A04A,C07F,N05B,C09B,A02B	19.663
9	J01M,C09X,N05B	J01M,C09X,N05B,A02B	19.615
10	C01D,A06A,N02B	C01D,A06A,N02B,A02B	19.397
11	C03D,R05D,C07F	C03D,R05D,C07F,A02B	19.029
12	A10A,R06A,M01A	A10A,R06A,M01A,A02B	18.421
13	B03X,R01A,C07F	B03X,R01A,C07F,A02B	18.301
14	V03A	V08C,B03X,V03A	18.275
15	V03A	V08C,V03A,B01A	17.706

Table 2: Top 15 OR Results for 1 ATC Code → 2 ATC Code

Rank	Antecedent ATC Code	Consequent ATC Code	Odds Ratio
1	V03A	V08C,V03A	16.077
2	D06B	D06B,N06A	15.643
3	V08C	V08C,V03A	10.5369
4	B03X	V08C,B03X	10.3946
5	D06B	D06B,A02B	10.110
6	V08C	V08C,B01A	9.6488
7	V08C	V08C,B03X	9.0679
8	J01C	J01C,M03B	8.606
9	R02A	R02A,M05B	8.5184
10	V08C	V08C,C07F	7.7568
11	V08C	V08C,C09B	7.5718
12	B01A	V08C,B01A	7.3581
13	N05A	R02A,N05A	7.3291
14	M01A	R02A,M01A	6.9336
15	V08C	V08C,A02B	6.8942

Figure 2. Drug network visualization. Significant odds ratios associated with baseline → two ATC combinations are shown by the edge's transparency within the network. The hub surrounding V08C, the hub at R02A, and the hub at H05A are highlighted and warrant further analysis.

4. Conclusions

- The directional drug interactions capture the ADE risks introduced by additional drugs taken on top of a set of baseline drugs. These patterns provide novel and valuable pharmacovigilance knowledge with potential to impact clinical decision support.
- We proposed an innovative computational framework to perform high order directional ADE effect analysis at the group level, where the Anatomical Therapeutic Chemical (ATC) codes were employed to define drug groups using their shared therapeutic properties.
- Our results indicate that ATC level groupings allow for targeted analysis on interesting drug subgroups, offering a new lens to interpret DDIs that could potentially lead to the discovery of previously unknown relationships.
- Our study has shown that by reducing all the complete ATC codes in the DDI data to a lower level, it is possible to investigate myopathy-inducing DDIs from a broader chemical scope than the traditional individual-drug analysis.
- Further biological and chemical analysis on our findings of myopathy-inducing group interactions could yield valuable insight on those respective groups and DDIs. In particular, these identified ADE signals are at higher-level and potentially easier to manage than those discovered at the individual level.

References:

1. Yao X, Tsang T, Qing Sun, Quinney S, Zhang P, Ning X, Li L, Shen L. (2020) Mining and visualizing high-order directional drug interaction effects using the FAERS database. BMC Medical Informatics and Decision Making, 20(Suppl 2):50.
2. Banda, J., Evans, L., Vanguri, R. et al. (2016) A curated and standardized adverse drug event resource to accelerate drug safety research. Sci Data 3, 160026.

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