A General Statistical Framework for Exploring FAERS

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Abstract

Automatic adverse event reporting databases such as FAERS are of critical importance in detecting safety signals for post-market drug surveillance. While there is much work on the detection of high reporting rates, analysis on detecting reporting disparities between different levels of covariates (such as race, sex, age) are slim, with previous works being mainly concerned with controlling such factors. As a result, data analysis on differences among covariate groups are usually limited to ad hoc methods. We propose a mathematical model for adverse event databases, along with hypothesis testing methods.

Introduction

FDA Adverse Event Reporting System (FAERS) database contains several million entries, each describes a case involving a drug usage, a resulting adverse events (AE), and information of patient involved. We can divide the data into separate subgroups based on factors such as age group and sex, and we are interested in formulating a method to detect reporting disparities for specific drug-AE combinations.

There are I AE's and J drugs of interest, the data can be restructured to give

- number of reports n_{ij} for the ith AE and jth drug
- n_{*j} as the sum of all reports for the jth drug, or the summation of n_{1j} to n_{Ij}
- Number of reports n_{ij} separated into $n_{ij}^{(1)}$ and $n_{ij}^{(2)}$ for subgroups of interest (1) or (2) (could be male/female, young/old), and similarly have n_{*j} separated into counts $n_{*j}^{(1)}$ and $n_{*j}^{(2)}$

Using this notation, a drug-AE combination without subgroup disparity would have $n_{ij}^{(1)}/\, n_{ij}$ be close to $n_{*j}^{(1)}/\, n_{*j}$ and $n_{ij}^{(2)}/\, n_{ij}$ be close to $n_{*j}^{(2)}/\, n_{*j}$. On the other hand, dissimilarities in these pairs of values would mean high subgroups disparities in reporting rates.

Mathematical Model

A probabilistic framework can be adapted from previous work in signal detection of FAERS-like databases. We specifically extend the model in Huang et al, which modeled drug-AE counts as Poisson variables: under the null hypothesis:

$$(n_{ij}^{(1)}, n_{ij}^{(2)}) \mid n_{ij}^{(1)}, n_{*j}^{(1)}, n_{*j}^{(2)}, n_{*j}$$
$$\sim multinomial(n_{ij},\ (n_{*j}^{(1)}/\, n_{*j}, n_{ij}^{(2)}/\, n_{*j}\ ))$$

This allows a variety of inferencing methods. We used a log-likelihood ratio statistic, normal approximations, and proportional reporting ratio as different methods of hypothesis testing.

	Small Difference					Medium Difference					Large Difference				
Small Sample	MLR ranked	MLR FDR	Normal FDR	Proportion Diff	PRR	MLR ranked	MLR FDR	Normal FDR	Proportion Diff	PRR	MLR ranked	MLR FDR	Normal FDR	Proportion Diff	PRR
Power	0.105	0.196	0.165	0.238	0.862	0.425	0.586	0.564	0.664	0.886	0.994	0.999	0.999	1	0.98
Sensitivity	0.0107	0.0147	0.0145	0.0204	0.0231	0.118	0.0774	0.0825	0.112	0.0351	0.863	0.48	0.507	0.561	0.0953
Precision	0.484	0.628	0.75	0.647	0.0984	0.505	0.847	0.908	0.854	0.141	0.408	0.92	0.953	0.925	0.298
Medium Sample															
Power	0.16	0.277	0.274	0.341	0.733	0.746	0.877	0.873	0.919	0.752	1	1	1	1	0.996
Sensitivity	0.0246	0.0278	0.0294	0.0381	0.0123	0.347	0.188	0.208	0.234	0.0269	0.91	0.635	0.669	0.674	0.11
Precision	0.514	0.766	0.819	0.786	0.0852	0.467	0.901	0.936	0.918	0.169	0.404	0.931	0.955	0.941	0.436
Large Sample															
Power	0.992	0.994	0.999	0.999	0.711	1	1	1	1	0.994	1	1	1	1	1
Sensitivity	0.527	0.293	0.327	0.33	0.0286	0.827	0.574	0.598	0.599	0.185	0.982	0.842	0.875	0.875	0.345
Precision	0.465	0.918	0.944	0.939	0.186	0.422	0.919	0.951	0.947	0.552	0.393	0.93	0.952	0.949	0.665

	MLR ranked	MLR FDR	Normal FDR	Proportion Diff	PRR
Small Sample	0.049	0.0973	0.0504	0.1094	0.8969
Medium Sample	0.0461	0.0751	0.0589	0.0824	0.8206
Large Sample	0.0473	0.0766	0.0653	0.0709	0.7787

noAE-young	noAE-old	AE-young	AE-old	
129	1143	8	4	Solifenacin
111	425	21	14	linezolid
208	304	45	16	Acyclovir
1052	1689	83	56	Cyclosporine
656	2161	29	23	Aspirin
863	3457	99	192	Metformin
1406	1029	122	30	olanzapine
3133	####	99	184	ambrisentan
####	####	277	172	Interferon beta-1a
2242	1736	3	35	Leuprolide
1418	1129	640	246	Acetaminophen

RESULTS

Simulations show several of our methods had good power and controlled type 1 error rates. Using the normal approximation, difference in proportion test, and likelihood ratio with FDR control has uniformly good results.

Conclusion

In simulations, our methodology detected statistically significant different reporting rates. Additionally, the methods were applied to the actual problems for drug safety, where we detected many signals that motivate further study on the mechanism of how certain drugs differently affect subgroups.

References

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