A Simulation-based Comparison of Drug-Drug Interaction Signal Detection Methods

Dagyeom Jung*, Inkyung Jung**
* Departments of Biostatistics and Computing, Yonsei University Graduate School
** Division of Biostatistics, Department of Biomedical Systems Informatics, Yonsei University College of Medicine

Introduction

Background

Many studies have proposed the methods to detect adverse event (AE) induced by taking two drugs together. They apply the statistical models to real world data and compared the performance. However, there are a few studies that carry out a simulation study to evaluate the performance. Also, the criterion used in each method to define signals is different and has pros and cons.

Purpose

We assess the performance of various detection methods by implementing simulation under various conditions. It allows us to find out that in what situation each of methods is useful. In addition, we can summarize and generalize the characteristics of each method.

A review of drug-drug interaction signal detection methods

◆ Notation

Table 1. Observed frequencies table for drug-drug-AE combination

Exposure status		AE status		Relative reporting rate
Drug1	Drug2	Yes	No	
No	No	a	b	$f_{00} = a/(a+b)$
Yes	No	c	d	$f_{10} = c/(c+d)$
No	Yes	e	f	$f_{01} = e/(e+f)$
Yes	Yes	g	h	$f_{11} = g/(g+h)$

1. Ω shrinkage method

We define $\mathrm{N} = \mathrm{g}$ as the observed report frequency, and $\mathrm{E} = g_{11} \cdot (\mathrm{g} + \mathrm{h})$ as the expected report frequency. The value g_{11} is defined as:

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

The Ω shrinkage measure is defined as $\Omega = log_2 \frac{N+\alpha}{E+\alpha}$. The lower limit of the 95% confidence interval for Ω can be estimated as follows:

$$\Omega_{025} = \Omega - \frac{\phi(0.975)}{\log(2)\sqrt{N}}.$$

The criterion $\boldsymbol{\Omega_{025} > 0}$ is used to determine drug-drug interaction (DDI) signal.

2. Chi-square statistics method

$$\mathrm{X} = \frac{N - E - 0.5}{\sqrt{E}}$$

The threshold **X>2** or **X>2.6** is set for identifying DDI signal.

3. Proportional reporting ratio (PRR)

$$PRR_{D1} = \frac{(c+g)/(a+d+g+h)}{(a+e)/(a+b+e+f)}$$
$$PRR_{D2} = \frac{(e+g)/(e+f+g+h)}{(a+c)/(a+b+c+f)}$$
$$PRR_{D1D2} = \frac{g/(g+h)}{(a+c+e)/(a+b+c+e+f)}$$

The lower bound of the 95% confidence interval for PRR is defined as:

$$PRR_{025} = e^{\ln PRR - 1.96SD}$$

where SD for Drug1, $SD_{D1} = \sqrt{\frac{1}{c+g} - \frac{1}{c+d+g+h} + \frac{1}{a+e} - \frac{1}{a+b+e+f}}$, for Drug2, $SD_{D2} = \sqrt{\frac{1}{e+g} - \frac{1}{e+f+g+h} + \frac{1}{a+c} - \frac{1}{a+b+c+d}}$, for Drug1-Drug2 pair, $SD_{D1D2} = \sqrt{\frac{1}{g} - \frac{1}{g+h} + \frac{1}{a+c+e} - \frac{1}{a+b+c+d+e+f}}$.

If $\boldsymbol{PRR_{025D1D2} > \max(PRR_{025D1}, PRR_{025D2})}$, then the drug pair is considered as a signal of DDI.

4. Concomitant signal score (CSS)

$$\text{Concomitant signal score (CSS)} = \frac{PRR_{025D1D2}}{\max(PRR_{975D1}, PRR_{975D2})}$$

The signal detection criteria are (1) $\boldsymbol{PRR_{025D1D2} > 1}$, (2) $\boldsymbol{CSS > 1}$ **.**

5. Additive model

The risk difference is defined as $RD_{AB} = f_{11} - f_{00}$, $RD_A = f_{10} - f_{00}$, $RD_B = f_{01} - f_{00}$. When $RD_{AB} > RD_A + RD_B$, the signal is detected. That is, f_{11}-f_{10}-f_{01}+f_{00} statistically significantly greater than 0 indicate a positive interaction. Therefore, we fit the linear probability model and test the interaction term.

$$P(Y=1) = \alpha + \beta_1 Drug1 + \beta_2 Drug2 + \beta_3 Drug1 * Drug2$$

When $\boldsymbol{\beta_3}$ **is statistically significantly greater than 0**, there is a potential drug-drug interaction.

6. Multiplicative model

The risk ratio is defined as $RR_{AB} = \frac{f_{11}}{f_{00}}$, $RR_A = \frac{f_{10}}{f_{00}}$, $RR_B = \frac{f_{01}}{f_{00}}$. When $RR_{AB} > RR_A \times RR_B$, the signal is detected. When $\frac{RR_{AB}}{RR_A \times RR_B}$ is statistically significantly different from 1, there is a signal of DDI. Likewise, we implement the log linear regression to test interaction term.

$$\log[P(Y=1)] = \alpha + \beta_1 Drug1 + \beta_2 Drug2 + \beta_3 Drug1 * Drug2$$

When $\boldsymbol{\beta_3}$ **is statistically significantly different from 0**, it is considered a potential drug-drug interaction.

Simulation study

Data generation

We generated data from a binomial distribution in each row of table 1. The incidence probability of adverse event p was set differently for each of scenarios. The data generation was repeated 3,000 times in each setting. We implemented simulation under the additive assumption.

In scenario 1, we assumed that there is no interaction under the additive assumption to evaluate the false positive rate. (1-1) was assumed that there is no effect of each single drug and no interaction. (1-2) was assumed that there is an effect of drug 2, but no interaction. (1-3) was assumed that there is an effect of drug 1 and drug2, but no interaction. (1-4) was assumed that the effect of drug 2 is greater than that of drug 1.

In scenario 2, we assumed that there is a positive interaction to evaluate sensitivity. (2-1) was assumed that there is an interaction but no effect of each single drug. (2-2) was assumed that there is an effect of drug 2, and interaction. (2-3) was assumed that there is an effect of drug 1 and drug2, and interaction. (2-4) was assumed that the effect of drug 2 is greater than that of drug 1.

Results

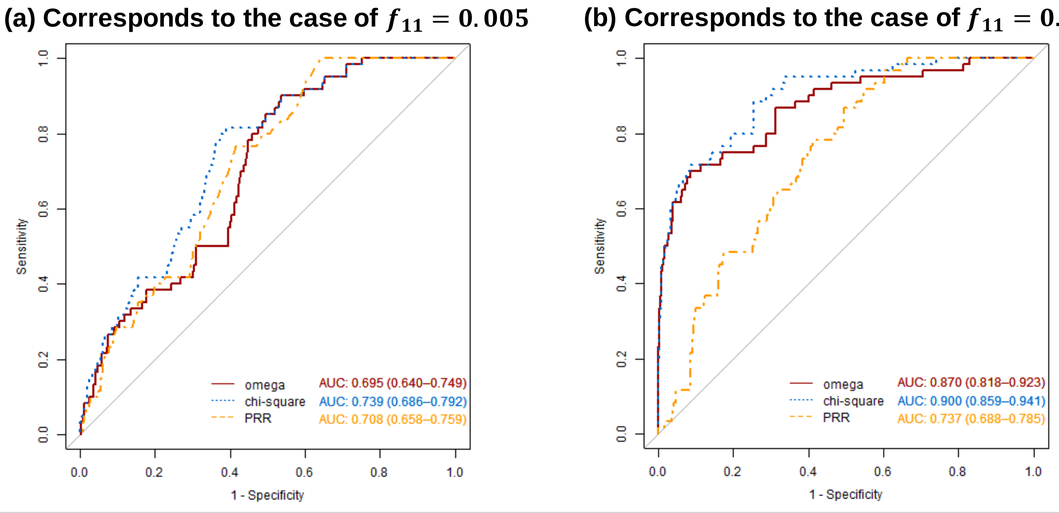
Additive assumption

Incidence probability for AE(%)						False positive rate						
						Ω shrinkage method	X^2 statistics method		PRR	CSS	Additive	Multiplicative
f_{00}	f_{10}	f_{01}	f_{11}	g	E		$X_{threshold=2}$	$X_{threshold=2.6}$				
Scenario 1-1												
0.005	0.005	0.005	0.005	1.5	1.4	0.008	0.013	0.005	0.012	0.003	0.001	0.065
0.05	0.05	0.05	0.05	6.0	7.2	0.007	0.006	0.002	0.017	0.005	0.020	0.055
0.5	0.5	0.5	0.5	50.9	55.3	0.001	0.001	0.000	0.010	0.004	0.029	0.037
Scenario 1-2												
0.001	0.001	0.005	0.005	1.5	0.9	0.031	0.049	0.025	0.013	0.002	0.001	0.003
0.01	0.01	0.05	0.05	6.0	6.5	0.032	0.028	0.008	0.013	0.008	0.016	0.027
0.1	0.1	0.5	0.5	51.0	53.4	0.003	0.003	0.000	0.006	0.002	0.031	0.026
Scenario 1-3												
0.001	0.003	0.003	0.005	1.5	0.8	0.039	0.066	0.029	0.083	0.004	0.001	0.002
0.01	0.03	0.03	0.05	5.9	5.1	0.054	0.048	0.015	0.127	0.051	0.011	0.000
0.02	0.05	0.05	0.08	8.9	8.1	0.055	0.049	0.017	0.114	0.074	0.019	0.000
Scenario 1-4												
0.002	0.003	0.006	0.007	1.7	1.1	0.045	0.058	0.029	0.029	0.005	0.001	0.008
0.002	0.003	0.015	0.016	2.6	2.0	0.046	0.053	0.023	0.023	0.005	0.006	0.002
0.002	0.003	0.03	0.031	4.1	3.6	0.050	0.045	0.017	0.006	0.001	0.009	0.000

Incidence probability for AE(%)						Sensitivity						
						Ω shrinkage method	X^2 statistics method		PRR	CSS	Additive	Multiplicative
f_{00}	f_{10}	f_{01}	f_{11}	g	E		$X_{threshold=2}$	$X_{threshold=2.6}$				
Scenario 2-1												
0.001	0.001	0.001	0.005	1.5	0.5	0.090	0.205	0.112	0.185	0.013	0.005	0.042
0.01	0.01	0.01	0.05	6.0	2.1	0.581	0.584	0.436	0.567	0.506	0.493	0.764
0.1	0.1	0.1	0.5	51.0	13.2	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Scenario 2-2												
0.001	0.001	0.002	0.005	1.5	0.6	0.075	0.140	0.084	0.094	0.011	0.002	0.024
0.01	0.01	0.02	0.05	6.0	3.0	0.332	0.329	0.218	0.387	0.244	0.252	0.409
0.1	0.1	0.2	0.5	51.1	23.0	0.999	0.999	0.994	1.000	1.000	1.000	1.000
Scenario 2-3												
0.001	0.002	0.002	0.005	1.5	0.6	0.069	0.119	0.069	0.118	0.008	0.001	0.011
0.01	0.02	0.02	0.05	5.9	3.2	0.293	0.284	0.170	0.368	0.185	0.110	0.089
0.1	0.2	0.2	0.5	51.0	28.4	0.986	0.983	0.939	1.000	1.000	0.973	0.409
Scenario 2-4												
0.001	0.002	0.004	0.008	1.8	0.8	0.102	0.133	0.076	0.157	0.013	0.005	0.006
0.001	0.002	0.03	0.05	6.4	3.5	0.250	0.240	0.136	0.051	0.014	0.110	0.000
0.1	0.15	0.25	0.5	50.9	28.9	0.986	0.981	0.928	0.995	0.995	0.976	0.557

We marked the value of FPR greater than 0.05 in red and the value of sensitivity greater than 0.80 in blue. Ω method and chi-square method with threshold=2 controlled the false positive rate below 0.05 and has high sensitivity in most of scenario. Especially, when the number of event (g) is small, the measure X has a higher sensitivity than Ω method. Comparing scenarios (2-3) and (2-4), the sensitivity of most methods decreases when f_{11} is the same but difference between the effects of the two drugs is large. On the other hand, the sensitivity of additive model is slightly increased or maintained.

(a) Corresponds to the case of $f_{11} = 0.005$ **(b) Corresponds to the case of $f_{11} = 0.05$**



Application

Data

We applied DDI signal detection methods to Korea Adverse Event Reporting System (KEARS) data from the Korea Institute of Drug Safety and Risk Management (KIDS) in 2017-2019. The known interaction was referred from the research report of Health Insurance Review and Assessment Service (HIRA) on adverse event monitoring system and the list of the contraindication of comedication drugs from KIDS (as of Dec. 28, 2020). And we selected several suspected interaction pairs from specific combination of drug-drug-AE that has high frequency.

Result

Table 2. The relative reporting rate in the exposure status of each drug-drug pair

Drug-Drug Pair	Adverse event	No A, No B	A, No B	No A, B	A and B
Known interaction					
potassium chloride-spironolactone	Hyperkalaemia	0.000	0.003	0.105	0.054
tacrolimus-spironolactone	Hyperkalaemia	0.000	0.028	0.103	0.063
domperidone-amiodarone	QT prolonged	0.000	0.001	0.016	0.222
Suspected interaction					
carvedilol-spironolactone	Hyperkalaemia	0.000	0.005	0.121	0.022
acetylsalicylic acid- polystyrene sulfonate	Hyperkalaemia	0.001	0.002	0.029	0.048
acetylsalicylic acid-amiodarone	QT prolonged	0.000	0.000	0.019	0.015

Table 3. The measure of each method applied to drug-drug / adverse event

Drug-Drug / Adverse event	Ω	X^2	PRR		CSS	Additive		Multiplicative	
			$PRR_{025d1d2}$	max		beta	p-value	beta	p-value
Known interaction									
potassium chloride-spironolactone / Hyperkalaemia	-1.780	-2.532	21.607	93.542	0.190	-0.053	0.001	-1.793	0.000
tacrolimus- spironolactone / Hyperkalaemia	-2.848	-1.250	11.371	93.542	0.010	-0.678	0.116	-3.951	0.000
domperidone-amiodarone / QT PROLONGED	1.062	5.741	382.197	57.637	3.096	0.205	0.037	1.001	0.185
Suspected interaction									
carvedilol-spironolactone / Hyperkalaemia	-3.135	-8.942	9.786	93.542	0.086	-0.104	0.000	-3.433	0.000
acetylsalicylic acid- polystyrene sulfonate / Hyperkalaemia	0.072	2.143	22.412	19.160	0.735	0.018	0.090	0.294	0.317
acetylsalicylic acid-amiodarone / QT PROLONGED	-1.749	-0.736	23.223	57.637	0.188	-0.004	0.614	1.511	0.183

The drug-drug / adverse event combination detected as a potential signal was marked in yellow and green. The drug-drug pair marked in yellow has very high incidence probability of AE. So AE induced by concomitant use is more likely to occur. The one in green has high frequency but has lower sensitivity in scenario (2-4) that has similar probability.

Conclusion & Discussion

Of the six methods, Ω method and chi-square method has the best performance. Chi-square method is especially good to use when AE has a small number of reports. The measure X with threshold=2.6 and Additive model are conservative method. They rigorously control the FPR. However, the aforementioned methods identify DDI by using a interaction signal indicator defined by equation. Therefore, there is a limitation in that the definition of true DDI signal depends on statistics.