

Estimation of the under-reporting in  
Japanese Adverse Drug Event Report Database and  
creation of a reference set to promote research of  
signal detection

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## **Abstract**

Background: Pharmacovigilance activities in the post-marketing phase are crucial because the safety information of drugs from the clinical trials prior to marketing authorization is often limited. Spontaneous reports of adverse drug reactions (ADRs) are a critical source of information for pharmacovigilance, but there is a problem of under-reporting. Recently, data mining methods have been developed to detect signals, which are potential ADRs, from the safety database. However, there is room for improvement in accuracy and adequacy of the methods, and further research is needed. Against such a background, this study was conducted with the aim of estimating the extent of under-reporting of serious ADRs (sADRs) in Japan (Research 1) and developing a reference set of data mining methods to improve signal detection based on the Japan safety databases (Research 2).

Method: In Research 1, new active ingredients approved in Japan between 2010 and 2016 for which all-case surveillance was conducted were selected. Data of sADR reports were extracted from the Japanese Adverse Drug Event Report database (JADER). An interrupted time series (ITS) analysis was conducted to compare the number of sADR reports obtained in the all-case surveillance period with that obtained in the spontaneous report period. In Research 2, a reference set was developed for a set of 43 drugs and 8 events. For each combination of the selected drug and event, those that were listed as important identified risks in the Japan Risk Management Plan (J-RMP) were set as “positive controls” and those that were not listed as adverse reactions anywhere in the package insert were set as “negative controls”. Also, we performed data mining using JADER and evaluated the results against the reference set to empirically confirm the effectiveness of the reference set.

Result: In Research 1, the ITS analysis of all sADR cases revealed that 24 (68.6%) of the 35 investigated drugs showed a statistically significant decrease in the intercept (level) in the spontaneous reporting period compared with that in the all-case surveillance period. The median of the reduction rate of the level was 60.1%. The number of drugs with a statistically significant decrease in the level of cases with sADRs in the Important Medical Event list and in that leading to death was 19/35(54.3%) and 6/35 (17.1%), respectively. In Research 2, a reference set was constructed including 89 positive controls and 177 negative controls. Comparison of the signals obtained from data mining using JADER with the reference set showed higher correlations than in previous studies.

Conclusion: This study suggested that under-reporting of adverse drug reactions occurred in JADER, but for fatal outcomes, the degree of under-reporting was relatively small compared to all serious ADRs. The reference set created in this research is reliable and is considered useful for conducting research for data mining methods with JADER. The results indicated that signals detected using JADER and this reference set are more likely to be true risks than those detected from other safety databases. Therefore, actively utilizing JADER as an important source of information for signal detection is considered beneficial.