Regular Article

Study on the Increased Probability of Detecting Adverse Drug Reactions Based on Bayes' Theorem: Evaluation of the Usefulness of Information on the Onset Timing of Adverse Drug Reactions

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Received February 22, 2017; accepted May 26, 2017; advance publication released online June 3, 2017

In order to avoid adverse drug reactions (ADRs), pharmacists are reconstructing ADR-related information based on various types of data gathered from patients, and then providing this information to patients. Among the data provided to patients is the time-to-onset of ADRs after starting the medication (*i.e.*, ADR onset timing information). However, a quantitative evaluation of the effect of onset timing information offered by pharmacists on the probability of ADRs occurring in patients receiving this information has not been reported to date. In this study, we extracted 40 ADR–drug combinations from the data in the Japanese Adverse Drug Event Report database. By applying Bayes' theorem to these combinations, we quantitatively evaluated the usefulness of onset timing information as an ADR detection predictor. As a result, when information on days after taking medication was added, 54 ADR–drug combinations showed a likelihood ratio (*LR*) in excess of 2. In particular, when considering the ADR–drug combination of anaphylactic shock with levofloxacin or loxoprofen, the number of days elapsed between start of medication and the onset of the ADR was 0, which corresponded to increased likelihood ratios (*LR*s) of 138.7301 or 58.4516, respectively. When information from 1–7 d after starting medication was added to the combination of liver disorder and acetaminophen, the *LR* was 11.1775. The results of this study indicate the clinical usefulness of offering information on ADR onset timing.

Key words Bayes' theorem; adverse event reporting system; adverse drug reaction; likelihood ratio; onset timing information; patient adherence instruction

One of the main tasks of a pharmacist who is engaged in dispensing drugs is to give instructions on the proper use of drugs to improve patient adherence. Article 25-2 of the Pharmacists Act requires pharmacists to provide necessary information and guidance based on pharmaceutical knowledge. Under this act, pharmacists have established a social standing as professional pharmaceutical advisers. We have recently reported the findings of an internet-based survey of 436 pharmacists and 562 patients on their opinion regarding the role of a pharmacist.[1)] We found that a role in "responsible monitoring of patients" was closely linked to the concept of pharmacists being "advisors on the use of pharmaceuticals." Regarding the "responsible monitoring of patients," there is a large gap between pharmacists and patients in terms of how they perceive the role of a pharmacist, indicating a role discrepancy. In addition, "responsible monitoring of patients" as a subordinate concept consists of "grasping the presence/absence of drug effectiveness," "changes in health status by drugs," and "consciousness to protect patients from adverse drug reaction (ADR)." The gap regarding role cognition between pharmacists and patients may disappear if adverse effects post administration of a medication and changes in patient health are found.

As one method to prevent the worsening of ADRs, when pharmacists are dispensing drugs they provide patients with information on the initial symptoms (ISs) of ADRs of the drug, so that patients can identify the onset of ADRs early and take the necessary action.[2)] A single ADR can often have multiple ISs, and among these ISs, there will be some that are more sensitive in predicting an ADR than others. In order to increase awareness regarding ADRs, we recently reported a quantitative evaluation method using Bayes' theorem that can be used to evaluate the usefulness of different ISs of an ADR.[3,4)] In one example, we looked at abnormal hepatic function, which is an ADR of terbinafine. The developed method was used to calculate likelihood ratios (*LR*s) for different ISs of abnormal hepatic function, and the calculated *LR* values were 5.17 for fever, 2.44 for nausea, and 1.43 for a rash, indicating that fever has the highest information value and is the most useful predictor of abnormal hepatic function following treatment with terbinafine.

In addition, Ghajar *et al.* have reported a method that can be used to increase the diagnostic probability of whether a rash that develops while taking sulfonamide is a sulfonamide-induced ADR or not.[5)] In this study, the authors analyzed five factors for prior odds using Bayes' theorem: (1) the patient's

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allergy history, (2) skin conditions, (3) the onset of a rash after taking the medication, (4) recovery after discontinuation of the treatment, and (5) the response to drug re-administration. They then calculated the posterior odds by multiplying the prior odds by the *LR*s of each of the above five factors, and reported that these factors increase the probability of a correct diagnosis. For example, in the case of a skin rash, if the onset of skin rash caused by sulfonamide is restricted to the beginning of treatment, onset timing information can contribute to an increase in the probability of identifying an ADR.

Accordingly, in this study, the concepts of prior probability, posterior probability, and likelihood ratio used in Bayesian statistics were applied to the identification and prevention of ADRs. Thus, when a specified ADR of a certain drug has a characteristic onset timing, confirmation of onset timing information by a pharmacist (treatment side), or the offering of this information to patients, can be expected to heighten the probability of discovering the ADR, with a certain likelihood ratio. In a similar study, without the use of likelihood ratios, safe administration of chemotherapy was successfully achieved by confirmation of ADR onset timing between the medical personnel and the patients.[6] With regard to the usefulness of likelihood ratios, Robert *et al.* state that "the information contributed by the test is summarized in one number corresponding to each level of test result. Additionally, likelihood ratios are particularly well suited for describing the overall odds of disease when a series of diagnostic tests is used."[7] Thus, the value of offering information can be quantitatively evaluated by employing likelihood ratios.[3,4] When applying Bayes' theorem to increase the ADR detection rate, the general onset probability of an ADR in the time elapsed since starting the medication is required as the prior probability, and the onset probability for a specific ADR–drug combination is required as the posterior probability. In order to obtain the general onset probability of an ADR, it is necessary to analyze many cases in order to guarantee the reliability of the analysis results. In this case, it is useful to analyze data from a large integrated ADR database or an adverse drug event reporting system database. Adverse event reporting system databases on the use of post-marketing drugs have already been established in the U.S.A., the U.K., the Netherlands, and Canada. In Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) has published data on reports of spontaneous adverse events (AEs) in Japan as the Japanese Adverse Drug Event Report database (JADER). A vast amount of information on more than 300000 AEs has been collected thus far in JADER. Because the JADER database contains time information, such as the medication start date, medication end date, and AE date, studies performing time analyses related to the onset of AEs have been reported.[8–10]

In this study, we examined the relationship between ADR onset timing information and posterior probability. According to our literature survey, no other studies have been reported that quantitatively examine the value of information provided to patients by applying Bayes' theorem to ADR onset timing information. This study quantitatively evaluated the usefulness of ADR onset timing information in an attempt to apply the concept of subjective probability to the work of community pharmacists.

THEORY

In general, the probability of whether or not a subject has a disease before undergoing an examination is expressed using the ratio of patients with that disease in the population, and this is defined as the prior probability. In the case of the examination result being positive and the patient being diagnosed with the disease, the probability that they really have contracted the disease is defined as the posterior probability. The usefulness of the diagnostic examination can then be evaluated, with a high posterior probability and a high ratio of posterior probability to prior probability (*i.e.*, a high *LR*) corresponding to a high usefulness. Bayes' theorem is a method of obtaining the morbidity probability of a patient by multiplying the likelihood ratio of the examination result by the prior odds. In this study, we used the posterior probability and *LR* to evaluate the usefulness of ADR onset timing information (*i.e.*, the time-to-onset of the ADR, referred to as Nday-onset-info), by considering the prior probability as the probability of an ADR occurring after taking a general medication, and the diagnostic examination as the ADR onset time information.

Likelihood Ratio Test Based on Bayes' Theorem Bayes' theorem is given by Eq. 1:

$$P(A \mid B) = \frac{P(B \mid A)P(A)}{P(B)} \tag{1}$$

where $P(A)$ is the probability of event A occurring, $P(B)$ is the probability of event B occurring, $P(A|B)$ is the posterior probability, and $P(B|A)$ is the likelihood. Converting Eq. 1 to odds by dividing Eqs. 1 by 2 gives Eq. 3.

$$P(A' \mid B) = \frac{P(B \mid A')P(A')}{P(B)} \tag{2}$$

$$\frac{P(A \mid B)}{P(A' \mid B)} = \frac{P(B \mid A)P(A)}{P(B \mid A')P(A')} \tag{3}$$

where A' is what is not event A.

Equation 3 can be expressed as Eq. 4 where A is the event that the patient has a disease (denoted disease +) and B is the event of a positive test result (denoted test +).

$$\frac{P(\text{disease}+ \mid \text{test}+)}{P(\text{disease}- \mid \text{test}+)} = \frac{P(\text{test}+ \mid \text{disease}+)P(\text{disease}+)}{P(\text{test}+ \mid \text{disease}-)P(\text{disease}-)} \tag{4}$$

Equation 4 can be expressed as:

$$Od_{\text{pos}} = LR \times Od_{\text{pri}}$$
$$LR = \frac{Od_{\text{pos}}}{Od_{\text{pri}}} \tag{5}$$

where LR is the likelihood ratio, Od_{pri} is the prior odds, and Od_{pos} is the posterior odds.

Further, the two-by-two contingency table of the survey data for obtaining Eq. 5 is shown in Table 1. From Eq. 5, the

Table 1. A Two-by-Two Contingency Table for Calculating the Likelihood Ratio

	Test-positive	Test-negative	Total
Disease	a	b	m
Normal	c	d	n
Total	$a+c$	$b+d$	$m+n$

likelihood ratio is given by the equation below:

$$\text{when } a \ll b, \text{ and } c \ll d,$$
$$LR = \frac{P(\text{test}+ \mid \text{disease}+)}{P(\text{test}+ \mid \text{disease}-)} = \frac{a/m}{c/n} = \frac{an}{cm} \quad (6)$$

where Eq. 6 is a risk ratio (RR) and therefore the risk ratio estimation method can be used. The risk ratio distribution can be normalized by log transformation.[11]

$$\ln(RR) \sim N(0, V_{\ln RR})$$

This property can be converted into an LR and used for estimation. The 95% confidence interval was estimated.[12]

$$V_{\ln(LR)} = \frac{1}{a} - \frac{1}{n} + \frac{1}{c} - \frac{1}{m}$$

lower limit:

$$e^{\left(\ln(LR) - 1.960\sqrt{V_{\ln(LR)}}\right)}$$

upper limit:

$$e^{\left(\ln(LR) + 1.960\sqrt{V_{\ln(LR)}}\right)}$$

Calculation of the Prior and Posterior Probability The incidence of an ADR occurring in a predetermined, arbitrary period of time for all of the ADRs recorded in the JADER database was defined as the prior probability (P_{pri}). In addition, for a specific drug–ADR combination, the probability of an ADR occurring during the same period as the prior probability was calculated and defined as the posterior probability (P_{pos}).

Calculation of Likelihood Ratios From Eq. 5:

$$LR = \frac{Od_{\text{pos}}}{Od_{\text{pri}}} = \frac{P_{\text{pos}}(1 - P_{\text{pri}})}{P_{\text{pri}}(1 - P_{\text{pos}})} \quad (7)$$

The LR can therefore be obtained by calculating the prior probability and the posterior probability.

METHODS

Data Sources The JADER database contains four types of data: the case list table ("demo"), the drug information table ("drug"), the ADR table ("reac"), and the primary disease table ("hist"). Each table is linked to "case identification numbers." The reason for drug administration registered in "drug," AE name registered in "reac," and primary disease name and complications registered in "hist" are based on the preferred terms (PTs) listed in ICH Medical Dictionary for Regulatory Activities/Japanese version (MedDRA/J). The version at the time of aggregation was unified in version 16.0. For the analysis in this study, "demo," "drug" and "reac" from April 2004 to June 2015 were downloaded from the PMDA website (http://www.info.pmda.go.jp/fukusayoudb/CsvDownload.jsp). Each downloaded table was concatenated using identification numbers to create a data frame. The data structure of the JADER database is in compliance with international safety reporting guidance, ICH E2B.

Data Cleaning Because the data reported to the JADER database includes duplicate and missing data, we cleaned the data frame.[13,14] First, "gender," "age," "weight," and "height" in "demo"; "drug name (general name)," "medication start date," and "medication end date" in "drug"; and "AE" and "AE date" in "reac" were all deleted as duplicate reports of the same cases. Next, we deleted reported cases where the "medication start date," "medication end date," or "AE onset date" data was missing. In this study, we wanted to estimate how much a pharmacist could improve the detection rate of ADRs when giving medication instructions in a community pharmacy. Hence, we extracted the cases in which the drugs involved were suspected of causing ADRs and were orally administered.

Targeted Combinations of ADRs and Drugs For convenience, we extracted the top ten ADRs from the obtained cleaned dataset. In addition, we extracted the top 10 types of drug for each of the top ten ADRs (*i.e.*, 100 types of ADR–drug combination in total). Among the 100 types of ADR–drug data extracted, those with a number of reported cases less than 100 were excluded from the calculation. Furthermore, in combinations where a specific drug had a high rate of concomitant use among the tested ADRs–drug, the effect of the concomitant drug on the ADR could not be ignored. For example, if there 100 reported cases of ADR-A occurring with drug-B, but in 50 of those cases drug-C was concomitantly used alongside drug-B, it can be inferred that drug-C has some effect on the onset of ADR-A. Therefore, for convenience, we excluded ADR–drug combinations involving specific drugs whose rate of concomitant use exceeded 20% from the calculation.

Time-to-Onset Analysis Utilizing *LR*s We calculated the number of days to ADR onset from the "medication start date" and the "AE onset date" in "reac" using Eq. 8.

$$\text{(Number of days to ADR onset)} = \text{(AE onset date)} - \text{(Medication start date)} \quad (8)$$

The ADR onset timing was calculated in intervals of general prescription days in Japan. The number of days to ADR onset was divided into nine predefined periods: (1) 0 (first day taking medication), (2) 1 to 7 d, (3) 8 to 14 d, (4) 15 to 30 d, (5) 31 to 60 d, (6) 61 to 90 d, (7) 91 to 180 d, (8) 181 to 365 d, and (9) 366 d or more. For each period, LR was calculated from P_{pos} (P_{pos0}, $P_{\text{pos1–7}}$, $P_{\text{pos8–14}}$, $P_{\text{pos15–30}}$, $P_{\text{pos31–60}}$, $P_{\text{pos61–90}}$, $P_{\text{pos91–180}}$, $P_{\text{pos181–365}}$ and $P_{\text{pos366+}}$) and P_{pri} (P_{pri0}, $P_{\text{pri1–7}}$, $P_{\text{pri8–14}}$, $P_{\text{pri15–30}}$, $P_{\text{pri31–60}}$, $P_{\text{pri61–90}}$, $P_{\text{pri91–180}}$, $P_{\text{pri181–365}}$, $P_{\text{pri366+}}$). We used the R Projects for Statistical Computing software package (R version 3.2.1, R Foundation for Statistical Computing, Vienna, Austria) for data processing.[15]

RESULTS AND DISCUSSION

ADR–Drug Combinations During data cleaning, the total number of reported cases decreased from 349375 to 115718 (number of drug–ADR combinations: 357497). Table 2 shows the 100 types of drug–ADR combinations extracted from the 115718 cases. The number of cases of these 100 combinations was 19493, which was equivalent to 16.85% (19493/115718) of the cleaned dataset. In Table 2, ★ represents a drug–ADR combination in which the rate of concomitant

Table 2. The 100 ADR–Drug Combinations Included in This Study

ID	ADR	Drug	ADR–drug abbreviation	Case number
1	Interstitial lung disease	Gefitinib	Il-Ge	783
2	Interstitial lung disease	Erlotinib hydrochloride	Il-Er	679
3	Interstitial lung disease	Methotrexate	Il-Me	545
4	Interstitial lung disease	Tegafur・Gimeracil・Oteracil potassium	Il-Tg	403
5	Interstitial lung disease	Everolimus	Il-Ev	348
6	Interstitial lung disease	Amiodarone hydrochloride	Il-Am	230
★ 7	Interstitial lung disease	Ribavirin		205
8	Interstitial lung disease	Loxoprofen sodium hydrate	Il-Lo	110
9	Interstitial lung disease	Imatinib mesylate	Il-Im	113
★10	Interstitial lung disease	Prednisolone		84
11	Hepatic function abnormal	Sorafenib tosylate	Hf-So	433
12	Hepatic function abnormal	Terbinafine hydrochloride	Hf-Tb	243
13	Hepatic function abnormal	Ticlopidine hydrochloride	Hf-Ti	191
14	Hepatic function abnormal	Loxoprofen sodium hydrate	Hf-Lo	180
★15	Hepatic function abnormal	Tegafur・Uracil		159
16	Hepatic function abnormal	Gefitinib	Hf-Ge	137
17	Hepatic function abnormal	Atorvastatin calcium hydrate	Hf-At	132
18	Hepatic function abnormal	Carbamazepine	Hf-Ca	130
19	Hepatic function abnormal	Fluvastatin sodium	Hf-Fl	117
20	Hepatic function abnormal	Lansoprazole	Hf-La	103
★21	Platelet count decreased	Ribavirin		486
22	Platelet count decreased	Sunitinib malate	Pc-Su	531
★23	Platelet count decreased	Simeprevir sodium		354
★24	Platelet count decreased	Tegafur・Gimeracil・Oteracil potassium		369
★25	Platelet count decreased	Lenalidomide hydrate		252
26	Platelet count decreased	Dasatinib hydrate	Pc-Da	215
27	Platelet count decreased	Sorafenib tosylate	Pc-So	166
28	Platelet count decreased	Everolimus	Pc-Ev	154
★29	Platelet count decreased	Dexamethasone		137
30	Platelet count decreased	Temozolomide	Pc-Tz	122
31	Anaphylactic shock	Levofloxacin hydrate	As-Le	139
32	Anaphylactic shock	Loxoprofen sodium hydrate	As-Lo	100
※33	Anaphylactic shock	Garenoxacin mesilate hydrate		96
※34	Anaphylactic shock	Cefcapene pivoxil hydrochloride hydrate		53
※35	Anaphylactic shock	Diclofenac sodium		44
※36	Anaphylactic shock	Eperisone hydrochloride		44
※37	Anaphylactic shock	Tosufloxacin tosylate hydrate		40
※38	Anaphylactic shock	Moxifloxacin hydrochloride		40
※39	Anaphylactic shock	Common cold remedy (over-the-counter drugs)		34
※40	Anaphylactic shock	Analgesic anti-inflammatory drugs (over-the-counter drugs)		32
★41	White blood cell count decreased	Ribavirin		557
★42	White blood cell count decreased	Simeprevir sodium		257
★43	White blood cell count decreased	Tegafur・Gimeracil・Oteracil potassium		310
★44	White blood cell count decreased	Telaprevir		268
45	White blood cell count decreased	Dasatinib hydrate	Wb-Da	171
46	White blood cell count decreased	Sunitinib malate	Wb-Su	152
47	White blood cell count decreased	Temozolomide	Wb-Tz	111
※48	White blood cell count decreased	Valganciclovir hydrochloride		96
※49	White blood cell count decreased	Prednisolone		79
※50	White blood cell count decreased	Procarbazine hydrochloride		88
51	Pyrexia	Lamotrigine	Py-Lm	282
★52	Pyrexia	Ribavirin		226
53	Pyrexia	Sorafenib tosylate	Py-So	111
54	Pyrexia	Carbamazepine	Py-Ca	104
★55	Pyrexia	Simeprevir sodium		94
※56	Pyrexia	Tegafur・Gimeracil・Oteracil potassium		86
※57	Pyrexia	Sunitinib malate		94
※58	Pyrexia	Mesalazine		89
※59	Pyrexia	Live Attenuated Human Rotavirus Vaccine, Oral		82
※60	Pyrexia	Loxoprofen sodium hydrate		61

Table 2. Continued

ID	ADR	Drug	ADR–drug abbreviation	Case number
★61	Neutrophil count decreased	Ribavirin		561
★62	Neutrophil count decreased	Tegafur・Gimeracil・Oteracil potassium		306
★63	Neutrophil count decreased	Lenalidomide hydrate		259
★64	Neutrophil count decreased	Telaprevir		194
★65	Neutrophil count decreased	Simeprevir sodium		152
66	Neutrophil count decreased	Dasatinib hydrate	Nc-Da	143
★67	Neutrophil count decreased	Dexamethasone		141
68	Neutrophil count decreased	Sunitinib malate	Nc-Su	103
※69	Neutrophil count decreased	Prednisolone		72
※70	Neutrophil count decreased	Temozolomide		72
71	Liver disorder	Terbinafine hydrochloride	Ld-Tb	196
72	Liver disorder	Ticlopidine hydrochloride	Ld-Ti	194
73	Liver disorder	Loxoprofen sodium hydrate	Ld-Lo	136
74	Liver disorder	Sorafenib tosylate	Ld-So	100
75	Liver disorder	Acetaminophen	Ld-Ac	102
※76	Liver disorder	Carbamazepine		94
※77	Liver disorder	Levofloxacin hydrate		89
※78	Liver disorder	Atorvastatin calcium hydrate		83
※79	Liver disorder	Fluvastatin sodium		87
※80	Liver disorder	Cefcapene pivoxil hydrochloride hydrate		80
★81	Anemia	Ribavirin		1321
★82	Anemia	Teraprevir		722
★83	Anemia	Simeprevir sodium		251
★84	Anemia	Lenalidomide hydrate		186
85	Anemia	Dasatinib hydrate	An-Da	167
★86	Anemia	Tegafur・Gimeracil・Oteracil potassium		147
87	Anemia	Everolimus	An-Ev	122
★88	Anemia	Dexamethasone		113
※89	Anemia	Sorafenib tosylate		83
※90	Anemia	Sunitinib malate		87
★91	Pneumonia	Methotrexate		262
★92	Pneumonia	Prednisolone		182
★93	Pneumonia	Tacrolimus hydrate		118
★94	Pneumonia	Lenalidomide hydrate		135
★95	Pneumonia	Dexamethasone		115
96	Pneumonia	Tegafur・Gimeracil・Oteracil potassium	Pn-Tg	100
※97	Pneumonia	Ciclosporin		54
※98	Pneumonia	Everolimus		54
※99	Pneumonia	Ribavirin		55
※100	Pneumonia	Mycophenolate mofetil		30

★: Combinations for which the rate of concomitant use of a certain drug exceeded 20%. ※: Combinations for which the number of reported cases was less than 100.

use of a certain drug exceeded 20%, and ※ represents combinations in which the number of reported cases was less than 100. There were 8598 cases (40 combinations) that were not marked with ★ and ※, accounting for 7.43% (8598/115718) of the cleaned dataset. These cases were taken forward for the subsequent calculations.

Interpretation of *LR*s Table 3 shows the calculation results of the 40 types of combinations targeted for calculation. The probability of an ADR being reported during each time period (P_{pri}) considering all of the ADR–drug combinations was $P_{pri0}=0.0605$ (21617/357497), $P_{pri1-7}=0.1838$ (65712/357497), $P_{pri8-14}=0.1116$ (39885/357497), $P_{pri15-30}=0.1446$ (51684/357497), $P_{pri31-60}=0.1358$ (48536/357497), $P_{pri61-90}=0.0697$ (24900/357497), $P_{pri91-180}=0.1026$ (36673/357497), $P_{pri181-365}=0.0815$ (29131/357497), and $P_{pri366+}=0.1101$ (39359/357497). *LR* was calculated from P_{pri} and P_{pos} in a preset period after taking the drug. As a result, it was clear that the onset timing of the same ADRs differs depending on the particular drug. For example, the timing of onset of interstitial lung disease was shown to be from 366 d onward after the start of treatment in the case of methotrexate and amiodarone hydrochloride, whereas in the case of gefitinib, erlotinib hydrochloride, tegafur/gimeracil/oteracil potassium, everolimus, loxoprofen sodium hydrate, and imatinib mesylate, interstitial lung disease occurs as an ADR within 90 d of starting treatment with the drug.

Three ADR–drug–onset timing (A–D–O) combinations showed an *LR* of more than 10. In these cases, onset timing information resulted in meaningful changes in the probability of identifying the occurrence of the ADR, which is considered to have considerable clinical value.[7,16] In all, there were 51 A–D–O combinations with an *LR* greater than 2 but less than 10. In these cases, ADR onset timing information could well have certain clinical value in terms of patient awareness of

Table 3. *LR* and 95% Confidence Interval for 40 ADR–Drug Combinations

ID	ADR–drug	Day	0	1–7	8–14	15–30	31–60	61–90	91–180	181–365	366+
	All	N	21617	65712	39885	51684	48536	24900	36673	29131	39359
		P_{pri}	0.0605	0.1838	0.1116	0.1446	0.1358	0.0697	0.1026	0.0815	0.1101
1	Il-Ge	N	3	109	125	209	141	85	51	30	30
		P_{pos}	0.0038	0.1392	0.1596	0.2669	0.1801	0.1086	0.0651	0.0383	0.0383
		LR	0.0598	0.7181	1.5128	2.1544*	1.3981	1.6266	0.6095	0.4491	0.3220
		95%CI	0.0193 to 0.185	0.6032 to 0.8548	1.2879 to 1.7770	1.9178 to 2.4202	1.2037 to 1.6239	1.3303 to 1.9889	0.4674 to 0.7949	0.3161 to 0.6380	0.2267 to 0.4574
2	Il-Er	N	1	116	107	160	132	76	60	21	6
		P_{pos}	0.0015	0.1708	0.1576	0.2356	0.1944	0.1119	0.0884	0.0309	0.0088
		LR	0.0229	0.9149	1.4896	1.8241	1.5361	1.6835	0.8480	0.3597	0.0721
		95%CI	0.0032 to 0.1623	0.7702 to 1.0868	1.2711 to 1.7457	1.6291 to 2.0425	1.3259 to 1.7796	1.3794 to 2.0546	0.6512 to 1.1043	0.2535 to 0.5105	0.0508 to 0.1023
3	Il-Me	N	1	4	12	15	37	50	131	98	197
		P_{pos}	0.0018	0.0073	0.0220	0.0275	0.0679	0.0917	0.2404	0.1798	0.3615
		LR	0.0286	0.0328	0.1793	0.1675	0.4636	1.3492	2.7682*	2.4713*	4.5757*
		95%CI	0.004 to 0.2027	0.0124 to 0.0871	0.1025 to 0.3138	0.1017 to 0.2759	0.3396 to 0.6328	1.0357 to 1.7576	2.3836 to 3.2148	2.0649 to 2.9576	4.091 to 5.1179
4	Il-Tg	N	0	20	24	57	111	79	50	34	28
		P_{pos}	0.0000	0.0496	0.0596	0.1414	0.2754	0.1960	0.1241	0.0844	0.0695
		LR	0.0000	0.2319	0.5043	0.9748	2.4198*	3.2569*	1.2391	1.0386	0.6035
		95%CI	Inf.	0.1513 to 0.3555	0.3421 to 0.7434	0.7663 to 1.2401	2.065 to 2.8356	2.6716 to 3.9704	0.9558 to 1.6064	0.7528 to 1.4329	0.4221 to 0.8628
5	Il-Ev	N	1	7	14	52	101	82	61	18	12
		P_{pos}	0.0029	0.0201	0.0402	0.1494	0.2902	0.2356	0.1753	0.0517	0.0345
		LR	0.0448	0.0912	0.3338	1.0395	2.6029*	4.1177*	1.8594	0.6148	0.2887
		95%CI	0.0063 to 0.3172	0.0438 to 0.1899	0.1998 to 0.5577	0.8089 to 1.3358	2.2081 to 3.0684	3.4065 to 4.9774	1.4802 to 2.3358	0.392 to 0.9642	0.1656 to 0.5034
6	Il-Am	N	2	11	10	21	28	17	23	45	73
		P_{pos}	0.0087	0.0478	0.0435	0.0913	0.1217	0.0739	0.1000	0.1957	0.3174
		LR	0.1363	0.2230	0.3620	0.5945	0.8824	1.0661	0.9720	2.7418*	3.7583*
		95%CI	0.0343 to 0.5418	0.1253 to 0.397	0.1974 to 0.6637	0.3954 to 0.8938	0.6235 to 1.2487	0.6746 to 1.6848	0.6595 to 1.4325	2.1093 to 3.564	3.1087 to 4.5436
8	Il-Lo	N	0	39	10	14	18	6	8	8	7
		P_{pos}	0.0000	0.3545	0.0909	0.1273	0.1636	0.0545	0.0727	0.0727	0.0636
		LR	0.0000	2.4391*	0.7963	0.8629	1.2454	0.7706	0.6861	0.8841	0.5493
		95%CI	Inf.	1.8953 to 3.1389	0.441 to 1.438	0.5289 to 1.4077	0.8162 to 1.9003	0.3539 to 1.6779	0.352 to 1.3373	0.4536 to 1.7232	0.2682 to 1.125
9	Il-Im	N	0	2	3	5	20	18	25	18	22
		P_{pos}	0.0000	0.0177	0.0265	0.0442	0.1770	0.1593	0.2212	0.1593	0.1947
		LR	0.0000	0.0800	0.2172	0.2739	1.3689	2.5309*	2.4853*	2.1358*	1.9541
		95%CI	Inf.	0.0203 to 0.316	0.0711 to 0.6634	0.1163 to 0.6453	0.9197 to 2.0374	1.6567 to 3.8664	1.7583 to 3.513	1.3981 to 3.2628	1.3429 to 2.8435
11	Hf-So	N	1	95	36	77	137	31	37	13	6
		P_{pos}	0.0023	0.2194	0.0831	0.1778	0.3164	0.0716	0.0855	0.0300	0.0139
		LR	0.0360	1.2480	0.7221	1.2798	2.9462*	1.0300	0.8174	0.3489	0.1136
		95%CI	0.0051 to 0.255	1.0447 to 1.4908	0.5281 to 0.9874	1.045 to 1.5674	2.5646 to 3.3845	0.7336 to 1.4462	0.6005 to 1.1126	0.2042 to 0.596	0.0513 to 0.2515
12	Hf - Tb	N	2	11	9	79	115	17	6	3	1
		P_{pos}	0.00825	0.0453	0.0370	0.3251	0.4733	0.0700	0.0247	0.0123	0.0041
		LR	0.1289	0.2105	0.3063	2.8503*	5.7191*	1.0048	0.2215	0.1409	0.0334
		95%CI	0.0324 to 0.5125	0.1182 to 0.375	0.1613 to 0.5816	2.3776 to 3.417	5.0073 to 6.532	0.6352 to 1.5894	0.1005 to 0.4882	0.0458 to 0.4339	0.0047 to 0.2362

Table 3. Continued

ID	ADR–drug	Day	0	1–7	8–14	15–30	31–60	61–90	91–180	181–365	366+
13	Hf-Ti	N	0	17	24	70	66	9	2	1	2
		P_{pos}	0.0000	0.0890	0.1257	0.3665	0.3455	0.0471	0.0105	0.0052	0.0105
		LR	0.0000	0.4338	1.1444	3.4230*	3.3610*	0.6605	0.0926	0.0593	0.0855
		95%CI	Inf	0.2756 to 0.6829	0.7871 to 1.6638	2.8402 to 4.1253	2.7646 to 4.0861	0.349 to 1.25	0.0233 to 0.3676	0.0084 to 0.4188	0.0215 to 0.3394
14	Hf-Lo	N	6	102	28	20	14	3	3	2	2
		P_{pos}	0.0333	0.5667	0.1556	0.1111	0.0778	0.0167	0.0167	0.0111	0.0111
		LR	0.5358	5.8066*	1.4669	0.7396	0.5369	0.2264	0.1483	0.1267	0.0908
		95%CI	0.2439 to 1.1768	5.1093 to 6.5991	1.0436 to 2.062	0.4892 to 1.1181	0.3246 to 0.888	0.0737 to 0.6954	0.0483 to 0.4555	0.0319 to 0.5027	0.0229 to 0.3603
16	Hf-Ge	N	0	7	5	24	69	9	10	9	4
		P_{pos}	0.0000	0.0511	0.0365	0.1752	0.5036	0.0657	0.0730	0.0657	0.0292
		LR	0.0000	0.2391	0.3016	1.2567	6.4592*	0.9392	0.6888	0.7926	0.2431
		95%CI	Inf	0.1162 to 0.492	0.1276 to 0.713	0.8738 to 1.8075	5.4688 to 7.6289	0.4994 to 1.7663	0.3792 to 1.2511	0.4215 to 1.4906	0.0926 to 0.6385
17	Hf-At	N	0	6	8	30	36	9	12	14	17
		P_{pos}	0.0000	0.0455	0.0606	0.2273	0.2727	0.0682	0.0909	0.1061	0.1288
		LR	0.0000	0.2114	0.5138	1.7403	2.3871*	0.9774	0.8748	1.3374	1.1949
		95%CI	Inf	0.0967 to 0.462	0.2625 to 1.0058	1.2705 to 2.3839	1.8065 to 3.1544	0.5201 to 1.8366	0.51 to 1.5005	0.8149 to 2.1949	0.7666 to 1.8624
18	Hf-Ca	N	0	17	15	45	43	4	3	1	2
		P_{pos}	0.0000	0.1308	0.1154	0.3462	0.3308	0.0308	0.0231	0.0077	0.0154
		LR	0.0000	0.6680	1.0387	3.1325*	3.1462*	0.4240	0.2067	0.0874	0.1263
		95%CI	Inf	0.4288 to 1.0406	0.6453 to 1.672	2.473 to 3.9679	2.4634 to 4.0183	0.1616 to 1.1128	0.0675 to 0.6326	0.0124 to 0.6158	0.0319 to 0.4997
19	Hf-Fl	N	6	8	7	32	46	10	4	1	3
		P_{pos}	0.0513	0.0684	0.2735	0.3932	0.0855	0.0342	0.0085	0.0256	1.0000
		LR	0.8399	0.3259	0.5067	2.2276*	4.1242*	1.2483	0.3097	0.0972	0.2127
		95%CI	0.3852 to 1.8313	0.167 to 0.6362	0.247 to 1.0393	1.6578 to 2.9932	3.2923 to 5.1662	0.69 to 2.2583	0.1182 to 0.8114	0.0138 to 0.6843	0.0696 to 0.65
20	Hf-La	N	5	31	19	14	15	8	9	2	0
		P_{pos}	0.0485	0.3010	0.1845	0.1359	0.1456	0.0777	0.0874	0.0194	0.0000
		LR	0.7927	1.9118	1.8012	0.9308	1.0850	1.1248	0.8376	0.2232	0.0000
		95%CI	0.3371 to 1.8641	1.4242 to 2.5663	1.1999 to 2.7037	0.5719 to 1.5148	0.6796 to 1.7323	0.5781 to 2.1885	0.4487 to 1.5636	0.0566 to 0.8805	Inf
22	Pc-Su	N	0	25	179	214	23	32	31	15	12
		P_{pos}	0.0000	0.0471	0.3371	0.4030	0.0433	0.0603	0.0584	0.0282	0.0226
		LR	0.0000	0.2194	4.0495*	3.9944*	0.2882	0.8566	0.5424	0.3277	0.1869
		95%CI	Inf	0.1496 to 0.3217	3.5929 to 4.5641	3.6005 to 4.4314	0.1932 to 0.4299	0.6121 to 1.1988	0.3854 to 0.7634	0.199 to 0.5397	0.1068 to 0.327
26	Pc-Da	N	4	72	24	53	23	7	18	8	6
		P_{pos}	0.0186	0.3349	0.1116	0.2465	0.1070	0.0326	0.0837	0.0372	0.0279
		LR	0.2946	2.2357*	1.0006	1.9358	0.7625	0.4495	0.7993	0.4356	0.2320
		95%CI	0.1116 to 0.7779	1.8516 to 2.6995	0.6862 to 1.4591	1.5322 to 2.4458	0.5182 to 1.122	0.2169 to 0.9316	0.5136 to 1.244	0.2207 to 0.8599	0.1054 to 0.5107
27	Pc-So	N	1	28	41	64	10	5	9	6	2
		P_{pos}	0.0060	0.1687	0.2470	0.3855	0.0602	0.0301	0.0542	0.0361	0.0120
		LR	0.0942	0.9009	2.6119*	3.7126*	0.4081	0.4148	0.5015	0.4227	0.0986
		95%CI	0.0133 to 0.6648	0.6426 to 1.2629	2.0023 to 3.4071	3.0634 to 4.4994	0.2238 to 0.7443	0.1749 to 0.9835	0.2656 to 0.9468	0.1927 to 0.9273	0.0249 to 0.391

Table 3. Continued

ID	ADR–drug	Day	0	1–7	8–14	15–30	31–60	61–90	91–180	181–365	366+
28	Pc-Ev	N	0	23	84	26	15	2	1	1	2
		P_{pos}	0.0000	0.1494	0.5455	0.1688	0.0974	0.0130	0.0065	0.0065	0.0130
		LR	0.0000	0.7796	9.5558*	1.2019	0.6869	0.1758	0.0572	0.0737	0.1064
		95%CI	Inf	0.5347 to 1.1366	8.2703 to 11.0411	0.8465 to 1.7065	0.4247 to 1.111	0.0444 to 0.6967	0.0081 to 0.4035	0.0104 to 0.5199	0.0269 to 0.4216
30	Pc-Tz	N	1	6	6	19	23	10	16	18	23
		P_{pos}	0.0082	0.0492	0.0492	0.1557	0.1885	0.0820	0.1311	0.1475	0.1885
		LR	0.1284	0.2297	0.4119	1.0915	1.4789	1.1926	1.3205	1.9509	1.8779
		95%CI	0.0182 to 0.9043	0.1053 to 0.5012	0.1888 to 0.8988	0.722 to 1.65	1.0233 to 2.1373	0.6585 to 2.16	0.8362 to 2.0852	1.2733 to 2.9891	1.2994 to 2.714
31	As-Le	N	125	12	0	1	0	0	0	1	0
		P_{pos}	0.8993	0.0863	0.0000	0.0072	0.0000	0.0000	0.0000	0.0072	0.0000
		LR	138.7301**	0.4196	0.0000	0.0429	0.0000	0.0000	0.0000	0.0817	0.0000
		95%CI	131.0271 to 146.8859	0.2443 to 0.7207	Inf	0.0061 to 0.3024	Inf	Inf	Inf	0.0116 to 0.576	Inf
32	As-Lo	N	79	11	2	6	0	0	0	1	1
		P_{pos}	0.7900	0.1100	0.0200	0.0600	0.0000	0.0000	0.0000	0.0100	0.0100
		LR	58.4516**	0.5488	0.1625	0.0000	0.0000	0.0000	0.0000	0.1139	0.0816
		95%CI	52.7899 to 64.7205	0.3142 to 0.9584	0.0412 to 0.6408	Inf	Inf	Inf	Inf	0.0162 to 0.8007	0.0116 to 0.5737
45	Wb-Da	N	3	57	18	32	17	14	13	10	7
		P_{pos}	0.0175	0.3333	0.1053	0.1871	0.0994	0.0819	0.0760	0.0585	0.0409
		LR	0.2775	2.2202*	0.9368	1.3622	0.7027	1.1911	0.7198	0.7001	0.3450
		95%CI	0.0904 to 0.852	1.7959 to 2.7447	0.6051 to 1.4503	0.9966 to 1.8619	0.4475 to 1.1034	0.7209 to 1.9679	0.4268 to 1.2139	0.3836 to 1.2776	0.167 to 0.7127
46	Wb-Su	N	0	8	29	79	4	8	15	7	2
		P_{pos}	0.0000	0.0526	0.1908	0.5197	0.0263	0.0526	0.0987	0.0461	0.0132
		LR	0.0000	0.2467	1.8775	6.4033*	0.1720	0.7241	0.9578	0.5442	0.1078
		95%CI	Inf	0.1257 to 0.4843	1.3531 to 2.6051	5.4947 to 7.4621	0.0654 to 0.4524	0.3688 to 1.4216	0.5923 to 1.5487	0.2639 to 1.1221	0.0272 to 0.4271
47	Wb-Tz	N	2	12	6	18	23	7	20	12	11
		P_{pos}	0.0180	0.1081	0.0541	0.1622	0.2072	0.0631	0.1802	0.1081	0.0991
		LR	0.2851	0.5382	0.4550	1.1452	1.6637	0.8990	1.9227	1.3663	0.8891
		95%CI	0.0722 to 1.1258	0.3154 to 0.9184	0.2089 to 0.9909	0.7502 to 1.7481	1.1561 to 2.3942	0.4388 to 1.8417	1.2928 to 2.8596	0.8006 to 2.3316	0.5074 to 1.5581
51	Py-Lm	N	2	21	107	78	62	3	4	3	2
		P_{pos}	0.0071	0.0745	0.3794	0.2766	0.2199	0.0106	0.0142	0.0106	0.0071
		LR	0.1110	0.3573	4.8689*	2.2624*	1.7939	0.1436	0.1259	0.1212	0.0577
		95%CI	0.0279 to 0.4417	0.2368 to 0.5392	4.1926 to 5.6543	1.8729 to 2.7329	1.4396 to 2.2354	0.0466 to 0.4426	0.0476 to 0.3331	0.0393 to 0.3736	0.0145 to 0.2296
53	Py-So	N	0	28	41	19	11	4	4	3	1
		P_{pos}	0.0000	0.2523	0.3694	0.1712	0.0991	0.0360	0.0360	0.0270	0.0090
		LR	0.0000	1.4980	4.6642*	1.2220	0.7002	0.4993	0.3270	0.3131	0.0735
		95%CI	Inf	1.0874 to 2.0637	3.6571 to 5.9487	0.8114 to 1.8403	0.3996 to 1.227	0.1907 to 1.307	0.1249 to 0.8559	0.1025 to 0.956	0.0104 to 0.5172
54	Py-Ca	N	0	13	36	27	18	2	3	1	4
		P_{pos}	0.0000	0.1250	0.3462	0.2596	0.1731	0.0192	0.0288	0.0096	0.0385
		LR	0.0000	0.6343	4.2158*	2.0748*	1.3323	0.2619	0.2598	0.1094	0.3233
		95%CI	Inf	0.3814 to 1.0548	3.2366 to 5.4912	1.4996 to 2.8706	0.8752 to 2.0281	0.0664 to 1.0333	0.0852 to 0.7924	0.0156 to 0.7694	0.1237 to 0.8452

Table 3. Continued

ID	ADR–drug	Day	0	1–7	8–14	15–30	31–60	61–90	91–180	181–365	366+
66	Nc-Da	N	3	46	14	28	19	10	12	9	2
		P_{pos}	0.0210	0.3217	0.0979	0.1958	0.1329	0.0699	0.0839	0.0629	0.0140
		LR	0.3330	2.1057*	0.8642	1.4407	0.9754	1.0043	0.8014	0.7571	0.1147
		95%CI	0.1085 to 1.022	1.6468 to 2.6924	0.5235 to 1.4267	1.0277 to 2.0197	0.6388 to 1.4893	0.5506 to 1.8317	0.4647 to 1.3822	0.401 to 1.4293	0.0289 to 0.4548
68	Nc-Su	N	0	1	11	44	15	6	18	6	2
		P_{pos}	0.0000	0.0097	0.1068	0.4272	0.1456	0.05825	0.1748	0.0583	0.0194
		LR	0.0000	0.0435	0.9521	4.4127*	1.0850	0.8262	1.8526	0.6972	0.1601
		95%CI	Inf	0.0062 to 0.3059	0.5446 to 1.6645	3.5279 to 5.5194	0.6796 to 1.7323	0.38 to 1.7962	1.2175 to 2.819	0.3207 to 1.5157	0.0406 to 0.6316
71	Ld-Tb	N	1	4	11	65	92	8	10	2	3
		P_{pos}	0.051	0.0204	0.0561	0.3316	0.4694	0.0408	0.0510	0.0102	0.0153
		LR	0.0797	0.0925	0.4735	2.9359*	5.6311*	0.5684	0.4703	0.1162	0.1256
		95%CI	0.0113 to 0.563	0.0351 to 0.244	0.2667 to 0.8408	2.4063 to 3.582	4.8512 to 6.5364	0.2883 to 1.1206	0.2571 to 0.8603	0.0293 to 0.4614	0.0409 to 0.3861
72	Ld-Ti	N	1	13	11	70	82	6	7	1	3
		P_{pos}	0.0052	0.0670	0.0567	0.3608	0.4227	0.0309	0.0361	0.0052	0.0155
		LR	0.0805	0.3189	0.4787	3.3402*	4.6605*	0.4263	0.3275	0.0584	0.1270
		95%CI	0.0114 to 0.5686	0.1886 to 0.5392	0.2696 to 0.8499	2.7692 to 4.0289	3.9529 to 5.4947	0.1939 to 0.9372	0.1582 to 0.6778	0.0083 to 0.4125	0.0413 to 0.3904
73	Ld-Lo	N	3	63	21	20	15	2	6	0	6
		P_{pos}	0.0221	0.4632	0.1471	0.1103	0.0147	0.0441	0.0000	0.0441	1.0000
		LR	0.3505	3.8321*	1.4541	1.0202	0.7891	0.1994	0.4038	0.0000	0.3731
		95%CI	0.1145 to 1.0733	3.1975 to 4.5927	0.9812 to 2.155	0.6806 to 1.5293	0.4895 to 1.272	0.0504 to 0.7892	0.1847 to 0.883	Inf	0.1706 to 0.8158
74	Ld-So	N	1	22	15	19	24	5	8	5	1
		P_{pos}	0.0100	0.2200	0.1500	0.1900	0.2400	0.0500	0.0800	0.0500	0.0100
		LR	0.1569	1.2524	1.4053	1.3879	2.0102*	0.7030	0.7607	0.5933	0.0816
		95%CI	0.0223 to 1.103	0.8658 to 1.8115	0.8812 to 2.241	0.9259 to 2.0804	1.4181 to 2.8494	0.2991 to 1.6521	0.3913 to 1.4788	0.2525 to 1.3943	0.0116 to 0.5737
75	Ld-Ac	N	6	73	13	3	3	1	1	1	1
		P_{pos}	0.0588	0.7157	0.1275	0.0294	0.0294	0.0098	0.0098	0.0098	0.0098
		LR	0.9711	11.1775**	1.1632	0.1793	0.1929	0.1323	0.0866	0.1116	0.0800
		95%CI	0.4468 to 2.1108	9.8887 to 12.6343	0.7 to 1.9329	0.0588 to 0.5467	0.0633 to 0.5882	0.0188 to 0.9303	0.0123 to 0.6089	0.0159 to 0.7847	0.0114 to 0.5625
85	An-Da	N	2	57	17	34	18	10	13	8	8
		P_{pos}	0.0120	0.3413	0.1018	0.2036	0.1078	0.0599	0.0778	0.0479	0.0479
		LR	0.1883	2.3009*	0.9025	1.5126	0.7690	0.8508	0.7385	0.5671	0.4067
		95%CI	0.0475 to 0.7467	1.8636 to 2.8409	0.5751 to 1.4163	1.1205 to 2.042	0.497 to 1.1898	0.4664 to 1.5519	0.4381 to 1.2448	0.2884 to 1.1152	0.2068 to 0.7998
87	An-Ev	N	4	6	15	22	27	23	16	7	2
		P_{pos}	0.0328	0.0492	0.1230	0.1803	0.2213	0.1885	0.1311	0.0574	0.0164
		LR	0.5267	0.2297	1.1163	1.3017	1.8092	3.1032*	1.3205	0.6861	0.1347
		95%CI	0.2009 to 1.3809	0.1053 to 0.5012	0.6949 to 1.7933	0.8916 to 1.9004	1.2968 to 2.524	2.147 to 4.4852	0.8362 to 2.0852	0.3342 to 1.4086	0.0341 to 0.5325
96	Pn-Tg	N	1	2	11	22	13	18	19	7	7
		P_{pos}	0.0100	0.0200	0.1100	0.2200	0.1300	0.1800	0.1900	0.0700	0.0700
		LR	0.1569	0.0906	0.9842	1.6689	0.9512	2.9321*	2.0521*	0.8484	0.6084
		95%CI	0.0223 to 1.103	0.023 to 0.3573	0.5635 to 1.7189	1.1538 to 2.4141	0.5728 to 1.5795	1.9294 to 4.4559	1.369 to 3.0761	0.4103 to 1.7128	0.2978 to 1.243

CI: Confidence interval, Inf: Infinite, **: $10<LR$, *: $2\leq LR\leq 10$

ADRs.[7,16] There were 68 A–D–O combinations with an *LR* of 1–2. Onset timing information for these A–D–O combinations is not likely to be clinically important.[7,16]

There were 54 A–D–O combinations with an *LR* greater than 2. In the case of these 54 combinations, onset timing information could be clinically useful. When we included the starting day of medication (*i.e.*, 0 d) as Nday-onset-info for the combination of anaphylactic shock with levofloxacin (Le) (ID 31 in Table 3) or loxoprofen (Lo) (ID 32 in Table 3), the *LR* was 138.7301 or 58.4516. Similarly, when we included the Nday-onset-info (*i.e.*, 1–7 d) for the combination of liver disorder with acetaminophen (Ac) (ID 75 in Table 3), the *LR* was 11.1775. This indicates that for these three combinations, onset timing information is clinically very useful.[16]

CONCLUSION

Using Bayes' theorem, we quantitatively evaluated the extent to which information on the days to onset of ADRs after taking drugs is clinically useful to patients in identifying ADRs. In the case of anaphylactic shock due to levofloxacin or loxoprofen administration, the results suggested that information on the number of days of using the drugs is extremely useful for patient awareness of the ADR. We also showed that for the combination of liver disorder and acetaminophen, the addition of onset timing information showed a high likelihood ratio. From the results of this study, the offering of ADR onset timing information to patients by pharmacists to raise patient awareness of ADRs, together with the recognition by pharmacists of characteristic onset timing information for ADRs with specific drugs, are clinically useful because patient monitoring of changes in their physical condition while taking medication can prevent ill effects associated with ADRs from becoming more serious.

Study Limitations The data analyzed in this study are held in a spontaneously reported adverse event database system. They are therefore subject to bias by under-reporting, and prone to the effects of the release of safety information by the regulatory authorities, and to market trends.

Conflict of Interest The authors declare no conflict of interest.

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