

Method for Detecting Drug-Induced Interstitial Pneumonia from Accumulated Medical Record Data at a Hospital

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Abstract Drug-induced interstitial pneumonia (DIP) is a serious adverse drug reaction. The occurrence rate of DIP was evaluated by clinical trial before available in the market. However, due to limited number of cases in clinical trials, it may be inapplicable to the real market. We aimed to seek a method to evaluate the occurrence rate of DIP using clinical data warehouse at a hospital. Initially we developed a method that assesses whether presence of IP was written in reports by natural language processing. Next we detected DIP by estimating IP before, during and after the drug administration. Presence of IP was determined according to the reports of CT if CT was performed, otherwise it was determined based on the changes in the results of chest X-ray, level of KL-6 or SP-D. DIP was determined according to the pattern of presence of IP in each phase. In this study we chose amiodarone as a target drug. The number of patients who suffered from IP caused by amiodarone was 16 (3.9 %), including one definitively diagnosed and 15 strong doubt cases. Most of them could be validated by medical record chart. Using this method, we were able to successfully detect occurrence of DIP from accumulated data in a hospital information system.

1 Introduction

Various adverse events occur related to medication use. Information regarding the risk of adverse events for each medicine is important for clinical practice. The safety of medicines is evaluated in clinical trials before the drugs are introduced into the market. However, because the number of subjects in clinical trials is limited, information regarding adverse events generated in clinical trials may be inadequate [1].

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Therefore, post-market pharmacovigilance is required for drug safety. Under the present circumstances, spontaneous reporting is the major method for gathering information about adverse events. This method is effective for detecting signals of the side effects of a drug; however, it is impossible to estimate the rate of occurrence of each side effect.

Recently, many hospitals have introduced electronic medical record systems, especially in Japan. Some of these systems include a clinical data warehouse (CDW) for the secondary use of the clinical data. Data relating to drug safety are expected to be included in CDW [2–6]. However, the raw data contained in the CDW are difficult to handle with respect to detecting adverse events.

In this study, we focused on drug-induced interstitial pneumonia which is one of the serious adverse drug reactions potentially terminated in death. Interstitial pneumonia (IP) is mainly diagnosed by chest CT, while chest X-ray, the sialylated carbohydrate antigen KL-6 (KL-6) and surfactant protein D (SP-D) levels are useful adjuncts to the diagnosis. We developed a method that detects the occurrence of IP using these data contained in CDW. Next, we devised a method to detect drug-induced IP (DIP) based on the timing of administration of the drug and occurrence or remission of IP. In this study, we chose amiodarone as a causal medicine of DIP. Amiodaron is one of the effective anti-arrhythmic drugs susceptible to DIP.

2 Methods

2.1 *Subject Data*

We used the text data of chest CT and chest X-ray reports and data of the KL-6 and SP-D levels contained in the CDW of Osaka University Medical Hospital from January 1, 2010 to March 31, 2013. The study protocol was approved by the Ethics Review Board of Osaka University Medical Hospital (Approval No. 13531, May 8th, 2014).

2.2 *Analysis of Chest CT and Chest X-Ray*

Each report of chest CT and chest X-ray consist of finding field and diagnosis field. Free text data are written in these fields. A radiologist inferred the diagnosis based on the findings of abnormalities. Initially we evaluated the data in diagnosis field and subsequently assessed the data in finding field when no definitive diagnosis could be obtained from data in the diagnosis field. The diagnostic data were searched for the keyword “interstitial pneumonia”. If IP was definitively diagnosed,

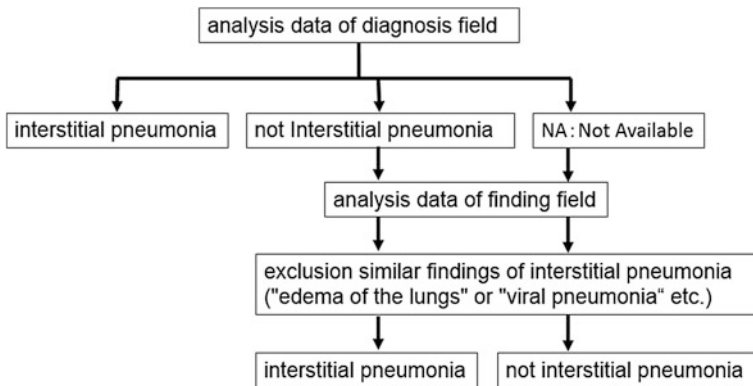


Fig. 1 Algorithm for detecting interstitial pneumonia using chest CT or X-ray reports

a flag for IP was set on the report. A synonym or detailed diagnosis of IP, such as “usual interstitial pneumonia (UIP)” or “acute interstitial pneumonia (AIP)”, was regarded as IP. When there was no definitive diagnosis, we then evaluated the data in the finding field. We searched for keywords in the finding data. Likelihood ratios of founded keywords are multiplied to obtain an IP score. A flag was set when IP score exceeded the cut-off value. There are some disease which have similar findings to those of IP, such as “edema of the lung” and “viral pneumonia”. There also are the cases of IP but not DIP, such as “lymphocytic interstitial pneumonia (LIP)” and “respiratory bronchiolitis-associated interstitial lung disease (RB-ILD)”. In these cases DIP should be denied, hence lower the flag if a flag for IP was set on the report (Fig. 1).

2.3 *Likelihood Ratios and Cut-off Values for Chest CT and X-Ray*

We selected 400 patients with interstitial pneumonia and 400 patients without interstitial pneumonia diagnosed by a radiologist using chest CT images from January 1, 2011 to March 31, 2013. Among these cases, 300 in each group were allocated to the learning dataset and 100 were allocated to the testing dataset (test data1). In addition, we selected 100 cases at random (test data2), which were not used for the learning data or test data1 sets. We also selected the data for chest X-ray obtained within three months from the chest CT. The learning data, test data1 and test data2 sets for chest X-ray (patients with and without interstitial pneumonia) included 354 cases (133, 221), 66 cases (24, 42) and 35 cases (4, 31), respectively. We extracted keywords from text data in the field of the chest CT reports for the training dataset. We used KHCoder to collect keywords [7] and selected words

appeared in more than 10 reports of IP. We calculated the likelihood ratio for a positive finding based on the frequency of each keyword. We also calculated the likelihood ratio for the learning dataset for chest X-ray. We handled abbreviations and detailed words, such as “UIP” (usual interstitial pneumonia) and “AIP” (acute interstitial pneumonia), and synonymous words, such as “frosted glass” and “ground glass”, as the same keywords. In cases that negative words, such as “not accepted” or “not confirmed”, in the neighborhood of a keyword, it was regarded as absence. Furthermore, in cases that there is a keyword but whose modifier is different from lung, such as “liver cyst” or “aortic calcification”, the keywords were regarded as absence. The likelihood ratios of the keywords appeared in a report were multiplied to determine IP score. We plotted ROC curve by changing cut-off point and obtained the nearest cut-off value to point (0, 1) on the ROC curve using test data1. We also evaluated the precision of the findings for detecting interstitial pneumonia using test data2.

2.4 *Detection of DIP*

We sought to detect cases of DIP caused by amiodarone in order to evaluate the proposing method. We used the reports of CT, X-ray and the level of KL-6 and SP-D obtained under treatment with amiodarone in the period from January 1, 2010 to December 31, 2013. The reports of chest CT and X-ray were judged to be positive or negative by the above-mentioned method. The KL-6 and SP-D levels were judged to be positive or negative according to the upper limit of normal values of each test. We then devised a method to determine the presence of IP before, during and after administration of amiodarone. The presence of IP was determined based on the reports of CT if CT was performed, otherwise it was determined according to the changes in the results of chest X-ray, the level of KL-6 or SP-D. In cases in which a judgment resulting from any of the reports of chest X-ray, the level of KL-6 or SP-D was the same as that of chest CT in a given phase, and the test judgement changed in another phase in which no chest CT findings, the test judgement was used as the judgement in its phase. For example, if the judgements of both chest CT and chest X-ray were “positive” during drug administration and “negative” by chest X-ray before drug administration, we noted that the assessment of chest X-ray was changed from “negative” before drug administration to “positive” during drug administration and judged the case as being “negative” before drug administration. The occurrence of DIP was judged using the five categories of “definitive”, “strongly suspected,” “weakly suspected,” “negative” and “judgment difficulty” based on the “positive,” “negative” and “not available” patterns of IP observed before, during and after drug administration (Table 1). For example, DIP was judged as being “strongly suspected” when the patterns of IP before, during and after drug administration were “negative,” “positive” and “positive”.

Table 1 Judgement of DIP based on the pattern of IP before, during and after drug administration (+: positive, -: negative, NA: not available)

Drug administration			Judgement
Before	During	After	
–	–	–	Negative
–	–	+	Negative
–	+	–	Definitive
–	+	+	Strongly suspected
+	–	–	Negative
+	–	+	Negative
+	+	–	Negative
+	+	+	Negative
NA	–	–	Negative
NA	–	+	Negative
NA	+	–	Strongly suspected
NA	+	+	Judgement difficulty
–	NA	–	Judgement difficulty
–	NA	+	Judgement difficulty
+	NA	–	Negative
+	NA	+	Negative
–	–	NA	Negative
–	+	NA	Strongly suspected
+	–	NA	Negative
+	+	NA	Negative
NA	NA	+	Judgement difficulty
NA	NA	–	Judgement difficulty
NA	+	NA	Weakly suspected
NA	–	NA	Negative
+	NA	NA	Negative
–	NA	NA	Judgement difficulty
NA	NA	NA	Judgement difficulty

2.5 Validation of DIP According to the Medical Records

We collected and checked the subjects’ medical records as to whether doctors thought DIP was induced by amiodarone. We therefore assessed the medical records of the patients who received amiodarone and checked whether “IP” was written in the medical records. We classified the case as involving “no description” if this information was not written. If the information for IP was provided, we checked the medical records as to whether IP was caused by amiodarone and classified the cases as “DIP”. “DIP suspected”, “DIP negative” or “no description”.

3 Results

3.1 Analysis of Chest CT and Chest X-Ray

The likelihood ratios for positive and negative findings for keywords related to chest CT using the learning data set are shown in Table 2. The keywords of “honeycombing”, “collagen” and “interstitial pneumonia” showed higher positive likelihood ratios. The likelihood ratios for positive and negative findings for keywords on chest X-ray using the learning dataset are shown in Table 3. The keywords of “reticular”, “interstitial pneumonia”, “ground-glass” and “dot-like” showed higher positive likelihood ratios. The cut-off value for chest CT using test data1 was 0.06 (sensitivity: 0.95, specificity: 0.98) and the cut-off value for chest X-ray was 0.012 (sensitivity: 0.83, specificity: 1). In addition, we assessed the detective precision of chest CT and chest X-ray for IP using test data2. The sensitivity was 0.89 and the specificity was 0.99 for the detective precision of chest CT, which were high. In terms of the detective precision of chest X-ray, the sensitivity was 0.67 and the specificity was 1.

Table 2 Keywords and likelihood ratios for chest CT

Keywords	Frequency of keywords			Likelihood ratio	
	Interstitial pneumonia		Total	Positive	Negative
	Positive	Negative			
Honeycomb	74	0.1	74	740.00	0.75
Collagen	14	0.1	14	140.00	0.95
Interstitial pneumonia	281	5	286	56.20	0.06
Traction bronchiectasis	140	3	143	46.67	0.54
Reticular	229	8	237	28.63	0.24
Diffuse	232	13	245	17.85	0.24
Reactivity	35	11	46	3.18	0.92
Convergence	17	6	23	2.83	0.96
Ground-glass	287	113	400	2.54	0.07
Cyst	44	23	67	1.91	0.92
Inspiratory	12	8	20	1.50	0.99
Infection	16	14	30	1.14	0.99
Curve linear	80	71	151	1.13	0.96
Calcification	57	52	109	1.10	0.98
Consolidation	29	27	56	1.07	0.99
Lymph node	35	33	68	1.06	0.99
Infiltration	22	21	43	1.05	1.00
Emphysema	52	53	105	0.98	1.00
Swelling	27	28	55	0.96	1.00
Nodular density	99	165	264	0.60	1.49
Band	48	81	129	0.59	1.15

(continued)

Table 2 (continued)

Keywords	Frequency of keywords			Likelihood ratio	
	Interstitial pneumonia		Total	Positive	Negative
	Positive	Negative			
Tuberculosis	11	19	30	0.58	1.03
Inflammatory	90	180	270	0.50	1.75
Heterogeneity	5	11	16	0.45	1.02
Cancer	23	59	82	0.39	1.15
Thick	23	59	82	0.39	1.15
Dot like	16	46	62	0.35	1.12
Cavity	3	9	12	0.33	1.02
Lung edema	4	12	16	0.33	1.03
Mass	15	51	66	0.29	1.14
Metastasis	7	41	48	0.17	1.13
Tumor	2	13	15	0.15	1.04
Atelectasis	4	49	53	0.08	1.18

Table 3 Keywords and likelihood ratios for chest X-ray

Keywords	Frequency of keywords			Likelihood ratio	
	Interstitial pneumonia		Total	Positive	Negative
	Positive	Negative			
Reticular	106	6	112	30.95	0.21
Interstitial pneumonia	86	6	92	25.11	0.36
Ground-glass	121	32	153	6.62	0.10
Dot like	13	13	26	1.75	0.96
Band	20	25	45	1.40	0.95
Curve linear	21	34	55	1.08	0.99
Permeability	7	14	21	0.88	1.01
Infiltration	5	11	16	0.80	1.01
Postoperative	11	25	36	0.77	1.03
Thick	14	40	54	0.61	1.08
Nodular density	14	42	56	0.58	1.09
Atelectasis	3	11	14	0.48	1.03
Calcification	2	10	12	0.35	1.03
Metastasis	2	10	12	0.35	1.03
Inflammatory	8	58	66	0.24	1.25

Table 4 Detection of DIP caused by amiodarone

Detection of DIP by this study	Chest CT	Chest CT, chest X-ray, KL-6, SP-D
Definitive	0 (0 %)	1 (0.2 %)
Strongly suspected	9 (2.2 %)	15 (3.6 %)
Weakly suspected	18 (4.4 %)	16 (3.9 %)
Negatively suspected	0 (0 %)	96 (23.2 %)
Negative	161 (39.0 %)	162 (39.2 %)
Judgement difficulty	225 (54.5 %)	123 (24.0 %)
Total	413 (100.0 %)	413 (100.0 %)

3.2 Determination of DIP

The number of patients who received amiodarone was 413 (prescription: 187, injection: 120, both: 106). The rate of “judgment difficulty” was 54.5 % when CT only was used, which was reduced to 24 % when added the results of chest X-ray, the level of KL-6 and SP-D secondarily. The judgement of DIP caused by amiodarone was “definitive” in one case (0.2 %), “strongly suspected” in 15 cases (3.6 %), “weakly suspected” in 16 cases (3.9 %), “negatively suspected” in 96 cases (23.2 %), “negative” in 162 cases (39.2 %) and “judgment difficulty” in 123 cases (24.0 %) (Table 4).

3.3 Validation of DIP According to the Medical Records

DIP descriptions in the medical records in each pattern of IP are shown in Table 5. Regarding the one patient who was judged as “definitive” based on the pattern of IP “negative”, “positive”, “negative” in phase of before, during and after drug administration respectively, “no description” was found in the medical record. In two of the three patients judged as “strongly suspected” with the pattern of “negative”, “positive” and “positive”, “DIP” was written in the medical records, while in the other case “DIP suspected” was written. In two of the three patients judged as “strongly suspected” with the pattern of “not available”, “positive” and “negative”, “DIP suspected” was written in the medical records; in the other case “no description” was written. For two of the nine patients judged as “strongly suspected” with the pattern of “not available”, “positive” and “negative,” “DIP suspected” was written in the medical records, whereas in the other case “no description” was found. Regarding the patients with a status of “negatively suspected” or “negative” with the pattern of “not available” in 3 phases, we considered these cases not to be DIP. The rate of DIP by amiodarone was 3.9 % if the “definitive” or “strongly suspected” cases assumed to be DIP.

Table 5 Validation of DIP according to the medical records (+: positive, -: negative, NA: not available)

Drug administration			Judge	The number of patients	DIP by medical records			
Before	During	After			DIP	DIP suspect	Negative	No description
-	+	-	Definitive	1				1
-	+	+	Strongly suspected	3	2	1		
NA	+	-	Strongly suspected	3		1		2
-	+	NA	Strongly suspected	9		2		7
NA	+	NA	Weakly suspected	16		4	4	8
-	-	-	Negative	16				16
-	-	+	Negative	1				1
+	-	-	Negative	3				3
+	-	+	Negative	2				2
+	+	-	Negative	0				0
+	+	+	Negative	0				0
NA	-	-	Negative	11				11
NA	-	+	Negative	1				1
+	NA	-	Negative	1				1
+	NA	+	Negative	1				1
-	-	NA	Negative	39			2	37
+	-	NA	Negative	6				6
+	+	NA	Negative	3				3
NA	-	NA	Negative	68			2	66
+	NA	NA	Negative	10				10
NA	+	+	Difficulty	1		1		
-	NA	-	Difficulty	23				23
-	NA	+	Difficulty	2				2
NA	NA	+	Difficulty	2				2
NA	NA	-	Difficulty	7				7
-	NA	NA	Difficulty	70				70
NA	NA	NA	Difficulty	114		1	3	110

4 Discussion

Because Image reports are written in free text, it is difficult to analyse these. We estimated certainty factor for IP of a reports by multiplying the likelihood ratios of the keywords appeared in a report. As the number of words characteristic of IP increased, the certainty factor for IP increased.

In order to detect DIP, it is necessary to estimate the presence of IP in phase of before, during and after drug administration. However, CT examinations were not so frequently performed, it is impossible to estimate the presence of IP in every phase only by CT. Thus we used the results of X-ray, the level of KL-6 or SP-D to estimate the presence of IP in each phase.

According to the package insert of amiodarone, the rate of DIP as a serious side effect in the field of internal medicine is 1.9 %; the rate for injections is unknown based on spontaneous reports. According to the results of this study, the rate of DIP induced by amiodarone is estimated to be 3.9 %, which is higher than the values shown in the package insert.

5 Conclusion

Using the method described in this study, we were able to successfully detect the occurrence of drug-induced interstitial pneumonia by using accumulated medical record data in a hospital information system.

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