—Regular Article—

Analysis of Body Constitution of Fifty-two Patients with Stevens-Johnson Syndrome (SJS) Using Kampo Medical Questionnaires: Prediction of SJS based on Body Constitution Using Decision Tree

Shigeru OHSHIMA,[a] Yukiko HATORI,[a] Seiichi HONMA,[b] Katsutoshi TERASAWA,[c] Yukiya SAITOH,[a] and Daisuke KOBAYASHI*,[a]

[a]*Department of Drug Informatics, Faculty of Pharmaceutical Sciences, Josai University, 1–1 Keyakidai, Sakado, Saitama 350–0290, Japan,* [b]*Onko-Do Kampo Akebono Yakkyoku Co., Ltd, 1–3–10, Gakuenhigashi-cho, Kodaira, Tokyo 187–0043, Japan, and* [c]*Department of Japanese Oriental "Kampo" Medicine, Department of Frontier Japanese Oriental "Kampo" Medicine, Graduate School of Medicine and School of Medicine, Chiba University, 1–8–1 Inohana, Chuo-ku, Chiba 260–8670, Japan*

(Received November 29, 2010; Accepted February 3, 2011; Published online February 8, 2011)

Reports have indicated a relationship between adverse drug reaction (ADR) and Human Leukocyte Antigen (HLA) polymorphism and a relationship between Body Constitution (BC) and HLA polymorphism. Thus, a relationship between ADR and BC is suggested. We therefore created a questionnaire (hereinafter "Questionnaire") to survey the typical BC of Stevens-Johnson Syndrome (SJS) patients to determine how they differ from healthy persons, and studied the relationship between the development of SJS and BC. The Questionnaire had 30 typical items selected from those relevant to the BC necessary for the diagnosis and therapy of Sho-syndrome in Kampo Medicine. In the comparison of the prevalence of BCs between SJS patients and control persons, the prevalence of three BCs in the SJS group was significantly higher than that in the control group: 1) Does your throat ever feel closed up? Answer: Yes, 2) Do you easily feel hot flashes or burning cheeks even though your hands and feet feel cold? Answer: Yes, and 3) Do your lips or gums look dull red? Answer: Yes. In the analysis using the decision tree, the concentrated group of SJS patients (eighty-fold) was extracted using two decision trees consisting of 3 index variables. Persons with BCs from any of 1) to 3) are suggested to be at high risk of developing SJS.

Key words——adverse drug reaction; body constitution; Stevens-Johnson syndrome; Kampo Medical Questionnaire; decision tree analysis

INTRODUCTION

Drug effects and adverse reactions are not dependent only on a drug class. They also depend on patient characteristics such as genetic polymorphisms of drug-metabolizing enzyme, transporter and receptor. These factors are considered causal explanations for individual differences of drug effects in recent years. Therefore, many studies at the genetic level for patient factors that influence drug effects have been reported.[1–6]

An early example of a report published as an alert is a report entitled Carbamazepine (marketed as Carbatrol, Equetro, Tegretol and generics), which was issued by the U.S. Food and Drug Administration (US FDA) on December 12, 2007.[7] This alert discussed a genetic level study of clinical drug therapy as follows: the manufacturers of drugs containing the active ingredient carbamazepine (CBZ) have agreed to add to the drugs' labeling a recommendation that before starting therapy with the drugs, patients with Asian ancestry should get a genetic blood test that could identify an increased risk of developing a rare, but serious, skin reaction, as Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).[8]

The alert is based on the report of Hung *et al*. and Lonjou *et al*. Hung and colleagues reported that SJS/TEN caused by CBZ is strongly associated with the Human Leukocyte Antigen (HLA)-B*1502 gene in Han Chinese.[1] Lonjou *et al*. reported that in a series of cases involving European patients with SJS/TEN associated with CBZ they found that patients who had Asian ancestry were over-represented, considering the small percentage of Asians in the general population. Of 12 patients, 4 were of Asian ancestry, and all 4 were positive for HLA-B*1502.[2]

The relevance of this is now similarly recognized in SJS/TEN of Thais or Indians.[4,5] In Japanese, how-

*e-mail: dkoba@josai.ac.jp

ever, there are no reports about the association between HLA-B*1502 gene and CBZ-induced SJS/TEN, though one report has indicated the association between allopurinol-induced SJS/TEN and HLA-B*5801.[6] Therefore, the relevance of the adverse effect by specific drugs to a genetic background is strongly suggested.

Alternatively, reports indicate the close connection of Body Constitution (BC) with certain HLA-gene types. Chen *et al*. studied the association between HLA Class II polymorphism and the classification of BC based on theories of Physical Constitution of Traditional Chinese Medicine (TCM): Normality, Yin-deficiency, Qi-deficiency, Wetness-heat, Yang-deficiency, Blood stasis and Phlegm-wetness. They reported that the allele frequencies of DPB1*0501 in the Yin-deficiency group, DRB1*09012 in the Phlegm-wetness group, and DQB1*3032 in Qi-deficiency and Phlegm-wetness groups were significantly high from that of the corresponding alleles in the Normality constitution in 706 individuals in the Han ethnic group in South China.[8]

This suggests that empirically classified BC in traditional medicine such as TCM and Kampo medicine based on TCM and adapted in Japan may be associated with genetic predisposition.

Since the relationship between adverse drug reaction (ADR) and HLA polymorphism, and the relationship between BC and HLA polymorphism have been reported, a relationship between ADR and BC (ADR/BC-Relationship) is suggested. For this reason, we searched the literature for an ADR/BC relationship in the Igaku Chuo Zasshi database and PubMed with MeSH keywords: body constitution and adverse drug event. We found no relevant articles.

In previous report, we studied the frequency and type of BC information described in the ADR case reports.[9] Since BC information was minimal, it was suggested that the study of the ADR/BC relationship using reported data was difficult at present. Under these circumstances, in order to investigate the ADR/BC relationship, we requested the participation of the SJS patient association. This association was the only association of patients with ADR that we could find listed on the Internet.

If we could discover the typical BC in SJS patients, which is different from healthy persons, such information might provide a key to elucidate the causal factor in developing SJS. Furthermore, the discovery might make the prevention of SJS possible.

Because there were no appropriate questionnaires to characterize ADR patients based on BC, we extracted a representative BC from the Kampo Medical Questionnaires used in the clinical setting.

To identify the characteristic BCs of SJS patients using Kampo Medical Questionnaires, 10 healthy persons were matched to 1 patient.

The age at which individuals developed ADR was different for each person, and the retrospective years of recall for BCs in the past from now to immediately before the onset was also different. Therefore, the matched items were age, sex and length of recall period.

METHODS

Preparation of Questionnaire The Questionnaire used for the BC survey was developed based on the items composing the Sho-syndrome, used in Kampo Medicine. These items refer to the BC itself. Sho-syndrome is composed of several types of BC.

On the occasion of diagnosis and therapy of Kampo Medicine, Sho-syndrome is scaled in view of Yin-Yang (陰陽), and classified into 6 different categories: Ki-kyo (気虚), ki-utsu (気鬱), Ki-gyaku (気逆), Ketsu-kyo (血虚), O-ketu (瘀血) and Sui-tai (水滞). Each BC item is given a score,[10] which is graded according to the contribution in determining Sho-syndrome.

Two specialists found high scored or typical 30 BCs in the 108 BCs that appeared in the Kampo Medicine textbook.[10] A few modifications (addition of items and change in score value) were made with narrowing down the items. Each question in the Questionnaire has a three-option answer: (1) yes, (2) yes, but only occasionally and (3) no. The Questionnaire is shown in Table 1. The classification and score value of each item are shown in Table 2.

Survey Methods

BC Survey of the SJS Patients In March 2008, Questionnaires were sent to the office of the SJS patient association (SJS Support Group, Yokosuka, Kanagawa, Japan) after explanation of the purpose of this study. The Questionnaires and prospectus were then sent to patients from the office of the SJS support group. Questionnaires completed by patients who agreed to participate in the study were returned to the office. We received the Questionnaires as

Table 1. Questionnaire

Fill in age, sex, suspect drugs that you remember, and the duration of drug exposure to onset that you remember.

Age	Sex	Onset age	Suspect drug(s)	Duration of drug exposure to onset
	M · F			

Read each question, and circle the answer that best describes your physical condition before onset and at present.

No.	Questionnaire items	Before onset	At present
1	Do you feel tired or easily fatigued?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
2	Do you feel a lack of will power?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
3	Do you feel you have a weak stomach?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
4	Do you have frequent diarrhea?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
5	Do you feel you are gloomy and easily depressed?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
6	Does your head feel heavy or is your thinking unclear?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
7	Does your throat ever feel closed up?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
8	Do you sometimes have a dry cough?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
9	Do you easily feel hot flashes or burning checks, even though your hands or feet feel cold?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
10	Do you feel palpitations, even when you remain motionless?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
11	Do you have frequent headaches?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
12	Does your face look pale?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
13	Do you sometimes have dry or rough skin, or do you easily get chapped skin?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
14	Are your fingernails fragile?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
15	Do you often become anemic?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
16	Is the amount of your menstrual blood minimal but the time prolonged?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
17	Do you easily get dark circles under eyes?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
18	Do your lips or gums look dull red?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
19	Do your capillaries easily stand out?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
20	Do you have hemorrhoids?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
21	Do you easily become swollen and do you easily notice the sound of water in your stomach?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
22	Do your hands feel stiff in the morning?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
23	Do you feel dizzy?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
24	Do you have a ringing in your ears?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
25	Are you sensitive to heat and fond of light clothing, and do you often sweat from the neck up?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
26	Do you drink a lot of cold water?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
27	Do you easily get a higher body temperature (above 36.7℃)?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
28	Are you sensitive to cold, and do your hands and feet feel cold, and do you like wearing thick clothes?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
29	Do you like a warm stimulus, such as electric blanket?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''
30	Do you easily get a lower body temperature (below 36.2℃)?	''No'' ''Yes, but only occasionally'' '' Yes''	''No'' ''Yes, but only occasionally'' '' Yes''

Thank you for your participation.

Table 2. Sho-syndrome Classification and Questionnaire Items Score Value

	Questionnaire items	Sho classification	Score value
Q1	Do you feel tired or easily fatigued?	Ki-kyo	10
Q2	Do you feel a lack of will power?	Ki-kyo	10
Q3	Do you feel you have a weak stomach?	Ki-kyo	10
Q4	Do you have frequent diarrhea?	Ki-kyo	4
Q5	Do you feel you are gloomy and easily depressed?	Ki-utsu	18
Q6	Does your head feel heavy or is your thinking unclear?	Ki-utsu	8
Q7	Does your throat ever feel closed up?	Ki-utsu	12
Q8	Do you sometimes have a dry cough?	Ki-utsu	8
Q9	Do you easily feel hot flashes or burning checks even though your hands or feet feel cold?	Ki-gyaku	14
Q10	Do you feel palpitations, even when you remain motionless?	Ki-gyaku	8
Q11	Do you have frequent headaches?	Ki-gyaku	8
Q12	Does your face look pale?	Ketsu-kyo	10
Q13	Do you sometimes have dry or sensitive rough skin, or do you easily get chapped skin?	Ketsu-kyo	14
Q14	Are your fingernails fragile?	Ketsu-kyo	8
Q15	Do you often become anemic?	Ketsu-kyo	6
Q16	Is the amount of your menstrual blood minimal but the time prolonged?	Ketsu-kyo	6
Q17	Do you easily get dark circles under your eyes?	O-ketu	10
Q18	Do your lips or gums look dull red?	O-ketu	5
Q19	Do your capillaries easily stand out?	O-ketu	5
Q20	Do you have hemorrhoids?	O-ketu	8
Q21	Do you easily become swollen and do you easily notice the sound of water in your stomach?	Sui-tai	15
Q22	Do your hands feel stiff in the morning?	Sui-tai	7
Q23	Do you feel dizzy?	Sui-tai	5
Q24	Do you have a ringing in your ears?	Sui-tai	5
Q25	Are you sensitive to heat and fond of wearing light clothing, and do you often sweat from the neck up?	Yin-yo	20
Q26	Do you drink a lot of cold water?	Yin-yo	10
Q27	Do you easily get a higher body temperature (above 36.7℃)?	Yin-yo	10
Q28	Are you sensitive to cold, and do your hands and feet feel cold, and do you like wearing thick clothes?	Yin-yo	−5
Q29	Do you like a warm stimulus, such as an electric blanket?	Yin-yo	−20
Q30	Do you easily get a lower body temperature (below 36.2℃)?	Yin-yo	−10

anonymous data. No information identifying patients was collected from the Questionnaires.

BC Survey of the Control Group We implemented the survey of the control group from October 28 to 29, 2009 through Internet research (Rakuten Research Inc. Company, Shinagawa, Tokyo, Japan). Participants were registered monitors of the Rakuten Research. Ten healthy persons were matched to one patient. The matched items were age, sex and length of recall period. The recall period was equal to the matched patient's period which was from the present to immediately before developing SJS. The control group answered the same items in the Questionnaire as either recalled or present (Table 1) on a computer display. For patients aged 10 to 15 years, parents provided surrogate responses. We received the anonymous data from Rakuten Research.

Analysis

Comparison of Prevalence of BC between SJS Group and Control Group The frequency of respondents who answered ''Yes'' and ''Yes, but only occasionally'' for each item was compared between the SJS group and control group using a chi-square test.

Calculation of Boundary Sho-score Which Gives Maximum Value of Positive and Negative Likelihood Ratio Both a Yin-Yang (陰陽) score and 6 categories of Sho-syndrome were calculated for each person. A boundary score for each Sho-syndrome that gives maximum value of positive and negative likelihood ratio between the SJS group and the control group was calculated.

Decision Tree Analysis Decision tree analysis investigated and extracted the condition of SJS

patients as compared to the control persons by comparing the presence or absence of a particular BC. Decision trees in which the first node was fixed every 30 items were built. Items (BCs) that appeared at depth 3 of the decision tree were used to construct an extraction. The analyses were performed by JMP5.1.2 (SAS Institute Japan) for Windows.

The Josai University Ethics Committee determined that this study met its standards because the data was anonymous.

RESULTS

Questionnaires Used for Analysis Sixty-nine Questionnaires were returned to us from the SJS support group office. Of the 69 Questionnaires, 12 were from SJS patients who developed SJS before 10 years of age. Because BC changes each year for those less than ten years old, recall is inaccurate. Therefore these patients were excluded from the analysis. Five Questionnaires were not completely filled in. Of the 69 Questionnaires returned, 17 were excluded from the analysis, and the remaining 52 were analyzed. Patient data (sex, age, age at development and time period of recall) are shown in Table 3.

The answers from 16 males and 36 females were analyzed. The mean age at the time of investigation was 45.7 years old (range: 18 to 76 years old). The mean age at the development of SJS was 30.6 years old (range: 10 to 59 years old). Since both the distribution and collection of the Questionnaires were performed by the SJS support group, the collection rate is unknown.

Comparison of Prevalence of BC between SJS Group and Control Group In comparing the prevalence of BC between the 52 cases of SJS group and the 520 persons in the control group, the prevalence (response rate of ''Yes, but only occasionally'' and ''Yes'') of 3 items in the SJS group were significantly higher than in the control group (chi-square test, $p<0.05$, Fig. 1); Q7 Does your throat ever feel

Table 3. SJS Patient Data

Patient No.	Sex	Age	Age at development	Time period of recall	Patient No.	Sex	Age	Age at development	Time period of recall
1	M	18	10	8	27	F	64	22	42
2	M	35	10	25	28	F	31	23	8
3	M	36	13	23	29	F	31	24	7
4	M	25	16	9	30	F	65	24	41
5	M	43	20	23	31	F	31	26	5
6	M	26	21	5	32	F	35	26	9
7	M	30	21	9	33	F	29	28	1
8	M	36	24	12	34	F	35	30	5
9	M	42	25	17	35	F	39	30	9
10	M	47	29	18	36	F	34	31	3
11	M	43	34	9	37	F	35	31	4
12	M	47	37	10	38	F	64	31	33
13	M	66	42	24	39	F	48	35	13
14	M	51	43	8	40	F	37	37	0
15	M	59	44	15	41	F	76	38	38
16	M	57	57	0	42	F	44	39	5
17	F	58	11	47	43	F	55	39	16
18	F	40	12	28	44	F	45	43	2
19	F	52	12	40	45	F	53	44	9
20	F	45	16	29	46	F	58	44	14
21	F	30	19	11	47	F	60	45	15
22	F	35	20	15	48	F	71	52	19
23	F	31	21	10	49	F	60	56	4
24	F	39	21	18	50	F	63	56	7
25	F	55	21	34	51	F	67	56	11
26	F	35	22	13	52	F	66	59	7

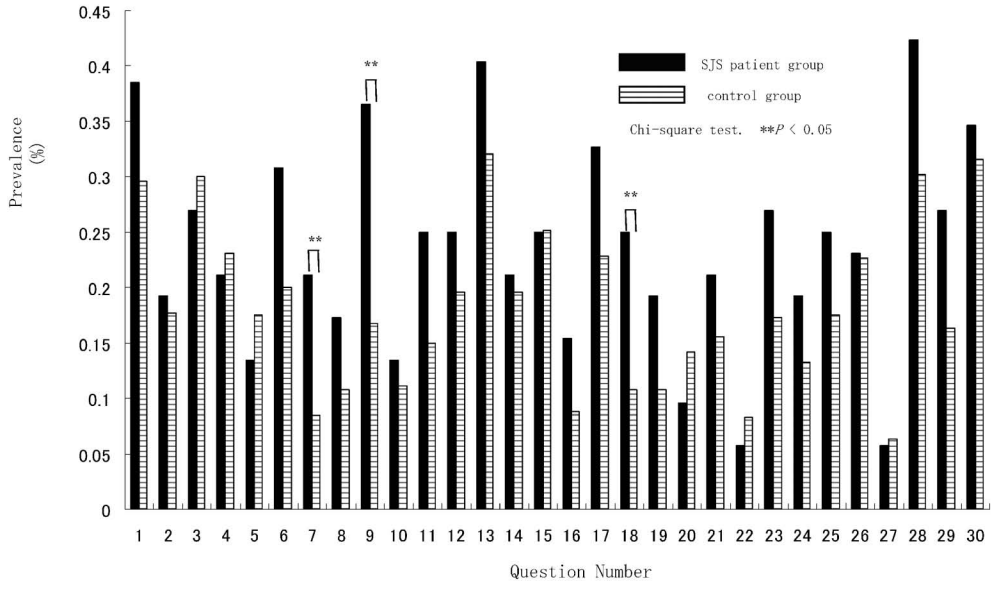

Fig. 1. Comparison of Prevalence of BC between SJS Group and Control Group

closed up?, Q9 Do you easily feel hot flashes or burning checks, even though your hands and feet feel cold? and Q18 Do your lips or gums look dull red?

Calculation of Boundary Sho-score Which Gives Maximum Value of Positive and Negative Likelihood Ratio The boundary Sho-score, which gives a maximum value of positive and negative likelihood ratio, is shown in Table 4. When the boundary O-ketu (瘀血) score was set at 22, the highest positive likelihood ratio 10.00 was observed. The number of persons exceeding this boundary value was one in the SJS group and one in the control group. The differences in the size (52 *vs.* 520) of the population which forms each group composed this result.

Next in order, positive likelihood ratios 8.00 and 7.5 were obtained by the boundary score of Ki-kyo (気虚): 30 and Ki-utsu (気鬱): 27, respectively. However sensitivities of both were low.

The highest negative likelihood ratio ranged from 0.90 to 1.36 in each Sho-syndrome. Therefore, the SJS group and the control group were not distinguished by the application of the Sho-score.

Decision Tree Analysis and Positive Likelihood Ratio The analytical results using the decision tree are shown in Table 5. In the first depth node, the items that create higher concentrated group of the SJS patients were Q7, Q9 and Q18. The prevalence of these items in the SJS group was significantly higher than in the control group.

An example of the decision tree in which the first depth node was fixed in Q7 (tree No. 7 in Table 5) is shown in Fig. 2. Question 7 showed the highest positive likelihood ratio of 2.50 in 3 items. The number of SJS patients in the first depth node was 11. The optimum second depth node determinant was Q18. The ''Yes'' node had 7 patients and the rate of SJS was 50 percent. The positive likelihood ratio was 10.

Similarly, the optimum third depth node determinant was Q21 Do you easily become swollen and do you easily notice the sound of water in your stomach? All five persons who answered ''no'' to this item were SJS patients.

In order to investigate the typical BC of SJS patients, we focused on the tree including the node which tentatively indicated the positive likelihood ratio of 10. These trees and the extracted SJS patients are shown in Table 6.

Since trees No. 7 and No. 18 are composed of the same three questions, tree No. 18 was not included in Table 6. SJS patients extracted in trees No. 7 and No. 24 did not overlap. Tree No. 7 specifically extracted 5 SJS patients and tree No. 24 extracted 3 female SJS patients based on Q16. Tree No. 24 indicated a positive likelihood ratio of 30.

Using the questions of trees No. 7 and No. 24, 8 SJS patients and 1 healthy person were extracted from all 572 persons studied. Erroneous extraction was only 1 from 572 persons studied. The positive likelihood ratio was 80.

Table 4. Boundary Sho-score with Maximum Value of Positive and Negative Likelihood Ratio in Each Sho-syndrome

Boundary Sho-score	LR(+) [95%CI]	LR(−) [95%CI]	Sensitivity	Specificity	Number of persons whose Sho-score is greater than boundary Sho-score	
					SJS patients (52)	Control group (520)
Ki-Kyo 30	**8.00** [2.20–29.1]	0.93 [0.89–1.01]	0.0769	0.9904	4	5
Ki-Kyo 18	1.09 [0.45–2.64]	**0.99** [0.92–1.07]	0.0969	0.9154	5	44
Ki-utsu 27	**7.50** [2.68–20.96]	0.90 [0.85–0.99]	0.1154	0.9846	6	8
Ki-utsu 37	2.50 [0.28–22.04]	**0.99** [0.96–1.02]	0.0192	0.9904	1	4
Ki-gyaku 20	**5.00** [1.55–16.16]	0.93 [0.89–1.01]	0.0769	0.9846	4	8
Ki-gyaku 24	2.50 [0.28–22.04]	**0.99** [0.96–1.02]	0.0192	0.9923	1	4
Ketsu-Kyo 31	**2.31** [0.67–7.89]	0.97 [0.92–1.03]	0.0577	0.9750	3	13
Ketsu-Kyo 2	0.67 [0.44–0.99]	**1.36** [1.05–1.45]	0.3462	0.4808	18	270
O-Ketu 22	**10.00** [0.63–158.4]	0.99 [0.96–1.02]	0.0192	0.9981	1	1
O-Ketu 16	1.43 [0.33–6.15]	**0.98** [0.95–1.04]	0.0385	0.9731	2	14
Sui-Tai 18	**3.33** [1.11–10.04]	0.94 [0.89–1.02]	0.0769	0.9769	4	12
Sui-Tai 22	1.25 [0.16–9.84]	**1.00** [0.97–1.03]	0.0192	0.9846	1	8
Yang-Sho 16	**2.19** [1.01–4.76]	0.92 [0.86–1.02]	0.1346	0.9385	7	32
Yang-Sho 26	1.00 [0.13–7.69]	**1.00** [0.97–1.03]	0.0192	0.9808	1	10
Yin-Sho 28	**2.31** [0.67–7.89]	0.97 [0.92–1.03]	0.0577	0.9750	3	13
Yin-Sho 31	1.25 [0.16–9.84]	**1.00** [0.97–1.03]	0.0192	0.9846	1	8

Maximum ratio is underlined.

DISCUSSION

Reports indicate the relationship between the occurrence of ADR and HLA polymorphism and the relationship between BC and HLA polymorphism, but there are few reports about the relationship between ADR and BC. Therefore, in order to identify the relationship between ADR and BC, the BC of patients developed a representative ADR of SJS were surveyed using BC Questionnaires and analyzed. The results were that Sho-syndrome, which is the original indication of classification of BC in Kampo Medicine and was used as an information source of BC, could not be classified into an SJS patient group and control group. However, the combination of patient BCs before SJS development could be classified into an SJS patient group and control group with high value of positive likelihood ratio. The reason classification was difficult was that abstraction from 108 BCs to 30 BCs considered the convenience of the respondent. This abstraction might impede the correct classification of Sho-syndrome.

SJS is a serious adverse effect caused by different kinds of drugs. Once SJS occurs, it can be associated with poor prognoses, disorders of the eyes and respiratory tract, and other health problems and may remain even after skin symptoms have been reduced.[11] As the occurrence frequency of SJS is extremely low, such as 1 to 6 individuals per million/year, SJS development is difficult to predict. Many

Table 5. Decision Tree Analysis and Positive Likelihood Ratio in Each Node

Tree No.	First depth node	Number of SJS patients	Number of control persons	LR+	Second depth node	Number of SJS patients	Number of control persons	LR+	Third depth node	Number of SJS patients	Number of control persons	LR+	SJS patient No.
1	Q1 Yes	20	145	1.30	Q9 Yes	12	51	2.35	age<24	5	6	8.33	20, 22, 26, 27, 28
2	Q2 Yes	10	92	1.09	Q7 Yes	6	19	3.16	Q18 Yes	5	5	10.00	13, 15, 20, 28, 35
3	Q3 No	37	364	1.02	Q9 Yes	9	73	1.23	Q24 No	4	7	5.71	16, 39, 42, 52
4	Q4 No	40	400	1.00	Q9 Yes	13	53	2.45	Q5 No	12	33	3.64	20, 23, 26, 28, 33, 36, 39, 42, 45, 49, 51, 52
5	Q5 No	44	429	1.03	Q9 Yes	15	52	2.88	Q12 Yes	8	15	5.33	11, 16, 28, 36, 39, 42, 51
6	Q6 Yes	16	104	1.54	Q7 Yes	8	21	3.81	Q18 Yes	5	6	8.33	13, 15, 20, 28, 35
7	Q7 Yes	11	44	2.50	Q18 Yes	7	7	10.00	Q21 No	5	0		10, 13, 15, 20, 26
8	Q8 Yes	9	56	1.61	Q18 Yes	6	12	5.00	Q13 No	4	1	40.00	15, 20, 35, 51
9	Q9 Yes	19	87	2.18	Q18 Yes	10	23	4.35	Q13 No	5	2	25.50	15, 20, 32, 35, 51
10	Q10 Yes	7	58	1.21	Q8 Yes	5	17	2.94	Q29 Yes	4	4	10.00	20, 35, 41, 44
11	Q11 Yes	13	78	1.67	Q17 Yes	10	32	3.13	Q29 Yes	8	10	8.00	13, 20, 26, 33, 38, 41, 44, 50
12	Q12 Yes	13	102	1.28	Q7 Yes	9	21	4.29	Q18 Yes	7	7	10.00	10, 13, 15, 20, 26, 28, 35
13	Q13 Yes	21	167	1.26	Q7 Yes	7	25	2.80	Q18 Yes	4	7	5.71	10, 13, 26, 28
14	Q14 Yes	11	102	1.08	Q11 Yes	8	34	2.35	Q7 Yes	4	8	5.00	13, 26, 28, 41
15	Q15 Yes	13	131	0.99	Q7 Yes	6	12	5.00	Q25 No	5	7	7.14	20, 26, 28, 29, 35
16	Q16 Yes	8	46	1.74	Q24 Yes	6	11	5.46	Q2 No	4	3	13.33	26, 33, 34, 40
17	Q17 Yes	17	119	1.43	Q23 Yes	11	35	3.14	age≧22	10	24	4.17	13, 26, 33, 34, 35, 38, 41, 42, 47, 48
18	Q18 Yes	13	56	2.32	Q7 Yes	7	7	10.00	Q21 No	5	0		10, 13, 15, 20, 26
19	Q19 Yes	10	56	1.79	Q9 Yes	9	27	3.33	Q29 Yes	7	8	8.75	32, 33, 35, 38, 41, 44, 50
20	Q20 No	45	446	1.01	Q9 Yes	17	67	2.54	Q18 Yes	9	17	5.29	11, 21, 27, 29, 33, 34, 36, 45, 52
21	Q21 Yes	11	81	1.36	Q20 No	11	54	2.04	Q13 No	6	11	5.46	12, 32, 35, 36, 47, 51
22	Q22 No	47	477	0.99	Q9 Yes	15	69	2.17	Q25 Yes	8	21	3.81	12, 22, 33, 38, 41, 48, 50, 51
23	Q23 Yes	14	90	1.56	Q17 Yes	11	35	3.14	age≧22	10	24	4.17	13, 26, 33, 34, 35, 38, 41, 42, 47, 48
24	Q24 Yes	10	69	1.45	Q16 Yes	6	11	5.46	Q5 No	3	1	30.00	34, 40, 41
25	Q25 Yes	13	91	1.43	age≧28	12	55	2.18	Q19 Yes	5	7	7.14	33, 38, 41, 48, 50
26	Q26 Yes	12	118	1.02	Q9 Yes	8	31	2.58	Q19 Yes	5	9	5.56	35, 38, 41, 44, 50
27	Q27 Yes	3	33	0.91	Q19 Yes	2	4	5.00	Analysis is completed in second depth node				35, 41
28	Q28 Yes	22	157	1.40	Q18 Yes	10	31	3.23	Q7 Yes	6	7	8.57	10, 13, 20, 26, 28, 35
29	Q29 Yes	14	85	1.65	Q18 Yes	8	16	5.00	Q20 No	7	8	8.75	13, 20, 26, 32, 33, 35, 44
30	Q30 Yes	18	164	1.10	Q18 Yes	7	27	2.59	Q29 Yes	7	10	7.00	13, 20, 26, 32, 33, 39, 44

LR+: positive likelihood ratio, Yes: answered ''Yes'' or ''Yes, but only occasionally'' to the questions.

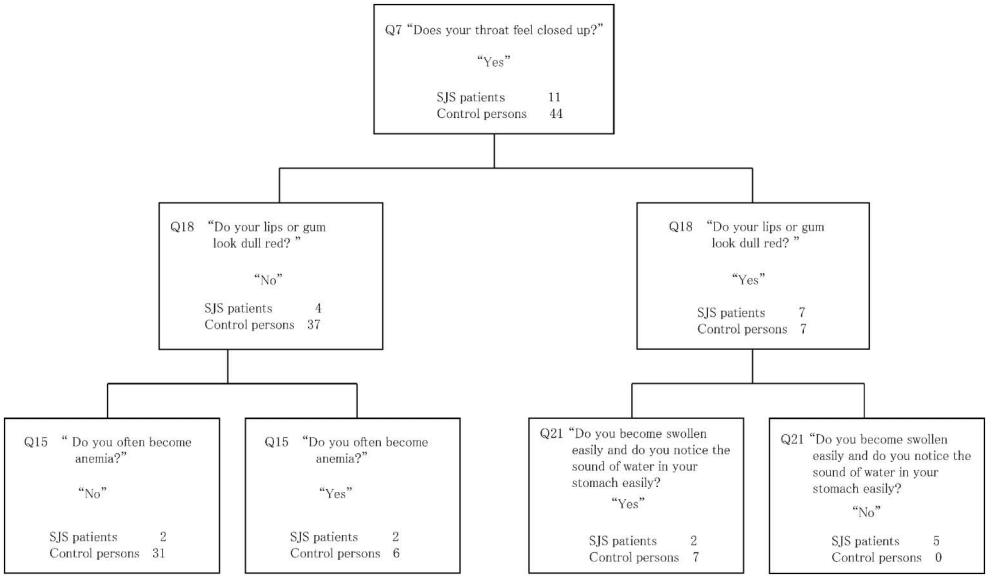

Fig. 2. Example of the Analysis Using Decision Tree (Tree No. 7)

reports, including epidemiologic reports,[12–16] address SJS, but no reports contribute to predicting SJS development. In Pharmaceuticals and Medical Devices Safety Information (PMDSI) published by Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare (MHLW), the proportion of SJS development to all ADR has increased from 1.3% (No. 163/November 2000) to 2.2% (No. 261/September 2009). Accordingly, MHLW has discussed the treatment and prevention of SJS.[17]

From the study results, patients extracted by trees No. 7 and No. 24 are considered at high risk of developing SJS. Also, having BCs described in Q7, Q9 and Q18 with prevalence significantly higher in SJS patients are indicative of SJS. This study proposed a novel method to predict SJS development based on BC. Further clinical practices to confirm the results of this study and to prevent ADR are our issues.

Next we discuss a causal connection between BC and pathogenesis before SJS development. SJS patients were extracted with a high value of positive likelihood ratio by combination of BCs selected as trees No. 7 and No. 24. However, only BCs selected as index variable by decision tree analysis are not always the specific BCs of SJS patients. If complex BCs are simultaneously present in all patients, the same extraction is possible by either BC. For example, 10 SJS patients of 13 SJS patients who have BC of Q18 have BC of Q9. Thus BC of Q9 was not selected as an index variable, and the BC was masked. However, prevalence of BCs described Q7, Q9 and Q18 were significantly higher in SJS patients. Hence these are characteristic BCs of SJS patients. Among these, your throat makes you feel closed up (Q7) is reported to be an early symptom of SJS.[11] There is a possibility that SJS patient mistakenly answered Q7 as BC before developing SJS. Therefore, identification is difficult in that it is intrinsic in BC or early symptoms. However, it was reconfirmed that Q7 is the alarming symptom or BC. We could not find any reports about ''your throat making you feel closed up'' related to developing SJS. Alternatively, ''Do you easily feel hot flashes or burning checks, even though your hands or feet are cold'' (Q9) and ''Do your lips or gums look dull red'' (Q18) possibly reflected a local ischemia or a disorder of peripheral blood flow. The relationship between the occurrence of SJS and a disorder of skin blood flow might require investigation.

The literature about the trigger for SJS/TEN examined the increase of trigger cells (CD94/NKG2C, HLA-DR$^+$D8$^+$) in peripheral blood flow.[18,19] A disorder of peripheral blood circulation is possibly a risk factor for increased concentration of trigger cells.

Study Limitations In this survey, an SJS patient group and a control group responded to questions about past BC recalling memories of 15.1 years earlier on average. Therefore it is necessary to consider the recall bias and reliability of memory. In general, the patient group remembered disease-associated past incidents clearly as compared with the

Table 6. Trees with Positive Likelihood Ratio Greater than 10

Tree No.		2	7	8	9	10	12	16	24
Questionnaire items	1st depth node	2 yes	7 yes	8 yes	9 yes	10 yes	12 yes	16 yes	24 yes
	2nd depth node	7 yes	18 yes	18 yes	18 yes	8 yes	7 yes	24 yes	16 yes
	3rd depth node	18 yes	21 no	13 no	13 no	29 yes	18 yes	2 no	5 no
Positive likelihood ratio		10	∞	40	25	10	10	13	30
SJS Patient No.	1								
	2								
	3								
	4								
	5								
	6								
	7								
	8								
	9								
	10		○				○		
	11								
	12								
	13	○	○				○		
	14								
	15	○	○	○	○		○		
	16								
	17								
	18								
	19								
	20	○	○	○	○	○	○		
	21								
	22								
	23								
	24								
	25								
	26		○				○	○	
	27								
	28	○					○		
	29								
	30								
	31								
	32				○				
	33							○	
	34							○	○
	35	○		○	○	○	○		
	36								
	37								
	38								
	39								
	40							○	○
	41					○			○
	42								
	43								
	44					○			
	45								
	46								
	47								
	48								
	49								
	50								
	51			○	○				
	52								

○ : extracted SJS patient.

control group.[20] Furthermore patients have a tendency to emphatically answer positively concerning exposure incidents which the patients think might have caused the disorder. In this study, the prevalence of BC in the SJS patient group (23.6%) was significantly higher than the control group (18.1%) ($p<0.01$). In 23 of 30 items, the prevalence of the SJS patient group was higher than the control group. The questions in which prevalence was significantly different in SJS patients (Q7, Q9 and Q18) were higher prevalence in SJS patients, so recall bias might exist. However it is highly unlikely that SJS patients answered these questions consciously as cause of SJS development. For example, an SJS patient who thought that having lips or gums look dull red (Q18) was pathogenesis of disease was the exception rather than the norm. Therefore, it seemed that the influence of recall bias was minimal. The fact that duration of recall was long might influence the reliability of results. In this study, 10 healthy persons were matched to 1 patient, and compared under the same conditions of sex, age and recall period. In spite of these conditions we thought that there might be some inaccuracy based on uncertain memory.

Acknowledgments We would like to thank the members of the SJS support group who contributed to this study.

REFERENCES

1) Hung S. I., Chung W. H., Jee S. H., Chen W. C., Chang Y. T., Lee W. R., Hu S. L., Wu M. T., Chen G. S., Wong T. W., Hsiao P. F., Chen W. H., Shih H. Y., Fang WH., Wei C. Y., Lou Y. H., Huang Y. L., Lin J. J., Chen Y. T., *Pharmacogenet Genomics*, **16**, 297–306 (2006).
2) Lonjou C., Thomas L., Borot N., Ledger N., de Toma C., LeLouet H., Graf E., Schumacher M., Hovnanian A., Mockenhaupt M., Roujeau J. C., *Pharmacogenomics J.*, **6**, 265–268 (2006).
3) Hung S. I., Chung W. H., Liou L. B., Chu C. C., Lin M., Huang H. P., Lin Y. L., Lan J. L., Yang L. C., Hong H. S., Chen M. J., Lai P. C., Wu M. S., Chu C. Y., Wang K. H., Chen C. H., Fann C. S., Wu J. Y., Chen Y. T., *Proc. Natl. Acad. Sci. USA*, **102**, 4134–4139 (2005).
4) Locharernkul C., Loplumlert J., Limotai C., Korkij W., Desudchit T., Tongkobpetch S., Kangwanshiratada O., Hirankarn N., Suphapeetiporn K., Shotelersuk V., *Epilepsia*, **49**, 2087–2091 (2008).
5) Mehta T. Y., Prajapati L. M., Mittal B., Joshi C. G., Sheth J. J., Patel D. B., Dave D. M., Goyal R. K., *Indian J. Dermatol. Venereol. Leprol.*, **75**, 579–582 (2009).
6) Kaniwa N., Saito Y., Aihara M., Matsunaga K., Tohkin M., Kurose K., Sawada J., Furuya H., Takahashi Y., Muramatsu M., Kinoshita S., Abe M., Ikeda H., Kashiwagi M., Song Y., Ueta M., Sotozono C., Ikezawa Z., Hasegawa R; JSAR research group. *Pharmacogenomics*, **9**, 1617–1622 (2008).
7) FDA News Release Administration: 〈http://www.fda.gov / Drugs / DrugSafety / PostmarketDrugSafetyInformationforPatientsandProviders/ucm124718.htm〉, cited 12 December, 2007.
8) Chen S., Lv F., Gao J., Lin J., Liu Z., Fu Y., Liu Y., Lin B., Xie Y., Ren X., Xu Y., Fan X., Xu A., *J. Altern. Complement. Med*, **13**, 231–239 (2007).
9) Oshima S., Oda A., Nemoto E., Dobashi A., Kobayashi D., Saitoh Y., Shirahata A., *Jpn. J. Drug Inform.*, **11**, 66–75 (2009).
10) Terasawa K., ''Syoureikaramanabu Wakanshinryougaku'' 2nd ed., Igakushoin, Tokyo, 1998.
11) Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, Pharmaceuticals and Medical Devices Safety Information, September 2009, No. 261, p. 3.
12) Roujeau J. C., Kelly J. P., Naldi L., Rzany B., Stern R. S., Anderson T., Auquier A., Bastuji-Garin S., Correia O., Locati F., Mockenhaupt M., Paoletti C., Shapiro S., Shear N., Erwin Schöpf E., Kaufman D. W., *N. Engl. J. Med.*, **333**, 1600–1607 (1995).
13) Hayakawa Y., Fumiko O., Yano R., Miwa I., Inagaki K., *Jpn. J. Pharm. Health Care Sci.*, **32**, 183–189 (2006).
14) Katahira K., Komatu Y., *Jpn. J. Drug Inform.*, **5**, 141–144 (2003).
15) Nassif A., Bensussan A., Boumsell L., Deniaud A., Moslehi H., Wolkenstein P., Bagot M., Roujeau J. C., *J. Allergy Clin. Im-*

munol., **114**, 1209–1215 (2004).
16) Nassif A., Moslehi H., Le Gouvello S., Bagot M., Lyonnet L., Michel L., Boumsell L., Bensussan A., Roujeau J. C., *J. Invest. Dermatol.*, **123**, 850–855 (2004).
17) Ministry of Health, Labour and Welfare, ''Jyutokufukusayo sikanbetu taiou manual,'' Vol. 1, Japan Pharmaceutical Information Center, Tokyo, 2007, pp. 5–19.
18) Morel E., Escamochero S., Cabañas R., Díaz R., Fiandor A., Bellón T., *J. Allergy Clin. Immunol.*, **125**, 703–710 (2010).
19) Nishio D., Izu K,. Kabashima K., Tokura Y., *J. Dermatol. Sci.*, **48**, 25–33 (2007).
20) Fransson E., Knutsson A., Westerholm P., Alfredsson L., *J. Clin. Epidemiol.*, **61**, 840–847 (2008).