

Exploring Factors Affecting the Occurrence of Hypersensitivity Reactions Induced by Nonionic Iodine Contrast Media

The Journal of Clinical Pharmacology
2023, 63(9) 1002–1008
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DOI: 10.1002/jcph.2256

Ryouichi Chatani, MSc¹, Sakura Kondo, BS¹, Tadamasa Kamimura, BS², Shinya Suzuki, PhD³, Eriko Komatsubara, BS², Seiichi Hayashi, BS², Masayuki Hashiguchi, PhD¹, Hayato Kizaki, MSc¹, Shungo Imai, PhD¹ , and Satoko Hori, PhD¹ 

Abstract

Hypersensitivity reactions induced by nonionic iodine contrast media sometimes occur and can be life threatening. However, independent factors affecting their occurrence remain to be fully established. Therefore, the purpose of this study was to clarify independent factors affecting the occurrence of hypersensitivity reactions induced by nonionic iodine contrast media. Patients who received nonionic iodine contrast media at Keiyu Hospital from April 2014 to December 2019 were included. The adjusted odds ratio (OR) and 95% confidence interval (CI) for factors affecting hypersensitivity reactions induced by contrast media were calculated by logistic regression analysis. The multiple imputation method was used to impute missing data. Hypersensitivity reactions occurred in 0.72% (163 cases) of 22,695 cases enrolled in this study. In univariate analysis, 10 variables met the criteria of $P < .05$ and proportion of missing data $< 50\%$. In multivariate analysis, age (OR, 0.98; 95% CI, 0.97–0.99), outpatient status (OR, 2.08; 95% CI, 1.20–3.60), contrast medium iodine content (OR, 1.02; 95% CI, 1.01–1.04), history of drug allergy (OR, 2.41; 95% CI, 1.50–3.88), and asthma (OR, 17.4; 95% CI, 7.53–40.1) were identified as independent factors affecting contrast media-induced hypersensitivity reactions. Among these factors, history of drug allergy and asthma appear to be clinically relevant and reliable due to their high OR and plausible biological mechanisms, but the other three factors require further validation.

Keywords

acute side effects, hypersensitivity reactions, independent factor, multivariate analysis, nonionic iodine contrast media

Radiological imaging data play an important role in medical diagnosis, and contrast media are widely used to enhance the contrast of lesions and tissues. However, acute side effects sometimes occur immediately after contrast media administration. These range from mild, such as nausea, vomiting, and urticaria, to life threatening and serious, such as cardiopulmonary arrest.^{1,2}

Nonionic contrast media have mainly been used in computed tomography examinations in recent years.² Nevertheless, 0.02%–3.0% of patients have been reported to develop side effects,^{1–6} and since there is often no alternative to iodine contrast media, managing the risk of developing side effects is an important clinical issue. The guidelines of the American College of Radiology⁶ include the following points of caution for the use of contrast media: (1) ensure that the administration of contrast is appropriate for the patient and the indication; (2) balance the likelihood of an adverse event with the benefit of the examination; (3) promote efficient and accurate diagnosis and treatment; and (4) be prepared to treat a reaction should one occur.

Although the mechanism of contrast media-induced adverse reactions is not fully understood, they

are pharmacologically classified as type A and type B reactions.^{7–9} Symptoms such as itching and skin rash are referred to as type B reactions (i.e., hypersensitivity reaction), and it is believed histamine and tryptase are involved in their pathogenesis. Symptoms such as nausea, vomiting, and headache are classified as

¹Keio University Faculty of Pharmacy, Minato-ku, Tokyo, Japan

²Department of Pharmacy, Kanagawa Prefectural Keiyukai Keiyu Hospital, Yokohama, Kanagawa, Japan

³Department of Pharmacy, Yokohama City Minato Red Cross Hospital, Yokohama, Kanagawa, Japan

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Submitted for publication 5 December 2022; accepted 23 April 2023.

Corresponding Author:

Satoko Hori, PhD, Division of Drug Informatics, Keio University Faculty of Pharmacy, 1-5-30 Shibakoen, Minato-ku, Tokyo 105-8512, Japan.

Email: hori-st@pha.keio.ac.jp

Ryouichi Chatani and Sakura Kondo contributed equally as co-first authors.

type A reactions. Since hypersensitivity reactions such as anaphylactic shock can be life threatening,⁶ it is important to identify factors affecting their occurrence in order to predict which patients may be at increased risk of contrast media-induced hypersensitivity reactions. However, predisposing factors for type B hypersensitivity reactions remain unknown.

Independent factors for the development of adverse effects to iodinated contrast media include a history of adverse effects to contrast media, history of bronchial asthma, and history of allergy to agents other than contrast media.^{10,11} Furthermore, several studies have reported factors affecting the occurrence of hypersensitivity reactions, though these remain controversial.^{12–16} Therefore, in this study, we aimed to identify independent factors affecting the development of hypersensitivity reactions after administration of nonionic iodine contrast media.

Materials and Methods

Ethical Considerations

This study was approved and conducted by the Research Ethics Committee for Human Subjects, Keio University Faculty of Pharmacy (Approval No. 201218-3).

Patient Selection

Patients who received nonionic iodine contrast media at Kanagawa Prefectural Keiyukai Keiyu Hospital from April 1, 2014, to December 31, 2019, were included in the study. In addition, only patients who received nonionic iodine contrast agent for the first time at the facility during the period were enrolled to avoid possible patient duplication and possible bias due to the potential clinical impact of the occurrence of hypersensitivity at previous administration (e.g., greater care in administration and closer observation). The nonionic iodine contrast agents are listed in Table S1.

Data Source

Acute side effects of nonionic iodine contrast media were defined as any side effects that occurred at the time of contrast media administration and were recorded by radiologists or other medical personnel. Among the recorded side effects, symptoms classified as allergic-like reactions (i.e., hypersensitivity reactions) in the guidelines of the ACR Manual on Contrast Media 2020 by American College of Radiology⁶ and the Guidelines on Contrast Agents Version 10.0 by the European Society of Urogenital Radiology⁵ were defined as the occurrence of hypersensitivity reactions to contrast media.

For the above subjects, the following information was extracted: basic information (age, sex, and weight), allergy history (contrast media, food, and drugs),

comorbidities (atopic dermatitis, urticaria, asthma, high blood pressure, diabetes, and dyslipidemia), laboratory data (blood urea nitrogen (BUN), serum creatinine (SCr), serum sodium, serum potassium, serum chlorine, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), blood glucose, glycated hemoglobin, white blood cell count, hemoglobin, platelet count (Plt), estimated glomerular filtration rate (eGFR) calculated according to the glomerular filtration rate estimation formula for Japanese,¹⁷ nonionic iodine contrast agent information (name of contrast agent, iodine content, presence of hypersensitivity reactions, and severity of hypersensitivity reactions), and premedication information. Since the aim of this study was to explore factors affecting the occurrence of hypersensitivity reactions, various laboratory data were evaluated. For each clinical item, data on the day of contrast agent administration were used. In the case of missing data on the day of contrast medium administration, the most recent data within 180 days before or after were used for weight, and the average of the data within 30 days before and after the day of contrast medium administration were used for laboratory data. Contrast medium iodine content was calculated from the contrast agent dosage listed in the electronic medical record. The severity of side effects, as judged by the physician, was extracted from the electronic medical record. Severity of hypersensitivity reactions was classified according to the Common Terminology Criteria for Adverse Events Version 5.0, that is:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to adverse reaction.

Premedication (prophylaxis) was defined as cases in which intravenous or oral steroid medication was administered on the day or 1 day before contrast medium administration.

Statistical Analysis

To compare the patients' characteristics between groups with and without hypersensitivity reactions, univariate analysis was performed. The Mann-Whitney *U*-test was used for factors that were continuous variables, and Pearson's chi-square test was used for factors that were

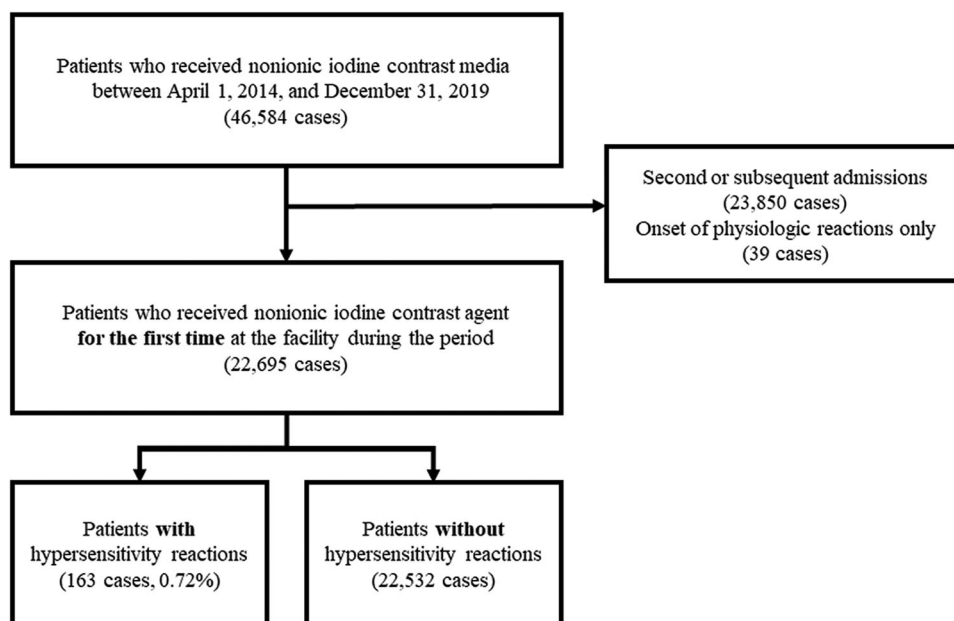


Figure 1. Extraction of analysis patients.

categorical variables. The proportion of missing data was calculated for each item.

Next, we performed logistic regression analysis to identify independent factors affecting the occurrence of hypersensitivity reactions using the forced imputation method. Independent variables were selected as factors that have been considered to affect the development of side effects in previous studies: history of contrast media allergy, asthma, dose, sex, age, and implementation of premedication, as well as factors with $P < .05$ in univariate analysis. The proportion of missing data of each factor was investigated, and factors for which the proportion of missing data was $\geq 50\%$ were excluded. Also, considering multicollinearity, variables with high Spearman's correlation coefficient ($r > 0.4$) were also excluded. At this time, the analysis was performed by applying the multiple imputation method, which is the most bias-suppressive method, to the factors with missing data among the factors that served as independent variables.¹⁸ In the multiple imputation method, the missing data are compensated by using a Markov chain stochastic process. Logistic regression analysis was conducted separately using five sets of missing data, and the statistical results were integrated to obtain the results of logistic regression analysis using the multiple imputation method.

In addition, a sensitivity analysis was performed using complete case analysis. In the complete case analysis, only those cases for which data were available for all factors were retained, and cases with missing data were removed from the analysis. In addition, logistic regression analysis was performed after the

classification of continuous variables into two values, above and below the cutoff value. The cutoff value was determined as the value that maximizes the Youden index calculated by receiver operating characteristic curve analysis.¹⁹

Statistical analysis was performed using IBM SPSS Statistics 26.0 (IBM Inc.) and Python 3.7 (Anaconda, Inc.).

Results

Study Patients and Univariate Analysis

The number of patients who developed hypersensitivity reactions was 0.72% (163 cases), and the number of those who did not was 22,532 (Figure 1). Among the patients who developed hypersensitivity reactions, Grades 1–4 occurred in 112 (68.7%), 46 (28.2%), 3 (1.84%), and 2 (1.23%), respectively. Due to the small number of patients with Grade 3 or higher, further analysis was not performed. Table 1 shows the results of univariate comparisons between the two groups.

The proportion of hypersensitivity reactions was 2.01% (44/2,194 cases) in patients who received Iomeprol, the contrast agent with the highest incidence proportion, followed by 0.86% (15/1,745 cases) in patients who received Ioversol. Details are provided in Table S2.

Compared to the patients without hypersensitivity reactions, those with hypersensitivity reactions had higher body weight, Plt, and eGFR. Also, the proportions of outpatients, history of drug allergy, and asthma were significantly higher in patients with hypersensitivity reactions. On the other hand, the group

Table 1. Univariate Comparison of Patient Background Factors between Groups With and Without Hypersensitivity Reactions.

Factors	With hypersensitivity reactions (n = 163)	Without hypersensitivity reactions (n = 22,532)	P value
Age (y), median (range)	55 (40–67)	64 (49–75)	<.001
Body weight (kg), median (range)	62.0 (52.4–72.2)	59.0 (50.3–68.0)	.042
Sex, n (%)			
Male	75 (46.0)	11,430 (50.7)	.230
Female	88 (54.0)	11,102 (49.3)	
Number of people using contrast media, n (%)			
Outpatient	146 (89.6)	18,361 (81.5)	.008
Inpatient	17 (10.4)	4,171 (18.5)	
Implementation of premedication, n (%)	2 (1.23)	79 (0.35)	.115
Iodine content, median (range)			
Contrast medium iodine content (g)	27.0 (27.0–30.0)	27.0 (27.0–30.0)	<.001
Contrast medium iodine content/bodyweight (g/kg)	0.48 (0.43–0.53)	0.47 (0.39–0.53)	.288
Clinical laboratory test, median (range)			
ALT (7–23 U/L)	17.0 (12.0–25.0)	18.0 (13.0–28.0)	.204
AST (13–30 U/L)	19.0 (15.5–24.5)	21.0 (17.0–28.0)	.002
BUN (8–20 mg/dL)	12.8 (10.0–15.0)	14.0 (11.0–18.0)	<.001
SCr (0.46–0.79 mg/dL)	0.71 (0.60–0.82)	0.74 (0.62–0.89)	.016
S-Cl (101–108 mmol/L)	105 (103–107)	104 (102–106)	.524
Glu (73–109 mg/dL)	105 (95.8–119)	110 (99.0–133)	.094
Hb (11.6–14.8 g/dL)	13.4 (12.0–14.7)	13.4 (12.2–14.6)	.683
HbA _{1c} (4.9–5.9%)	5.9 (5.6–7.6)	5.9 (5.5–6.6)	.512
S-K (3.6–4.8 mmol/L)	4.2 (3.9–4.4)	4.1 (3.9–4.4)	.287
LDH (124–222 U/L)	172 (153–193)	188 (164–220)	<.001
S-Na (138–145 mmol/L)	140 (139–142)	140 (138–142)	.288
Plt (158–348 × 10 ³ /μL)	231 (196–286)	223 (182–269)	.041
T-bil (0.4–1.5 mg/dL)	0.70 (0.55–1.00)	0.80 (0.60–1.00)	.379
WBC (3.3–8.6 × 10 ³ /μL)	6.60 (5.10–8.90)	6.70 (5.30–9.00)	.648
eGFR (mL/min/1.73 m ²)	78.5 (68.8–87.3)	72.6 (61.0–85.1)	.001
Allergy, n (%)			
Drug allergy	22 (13.5)	1,452 (6.44)	<.001
Contrast media allergy	3 (1.84)	183 (0.81)	.150
Food allergy	7 (4.29)	700 (3.11)	.384
Comorbidity, n (%)			
Atopic dermatitis	0 (0)	9 (0.04)	1.00
Asthma	7 (4.29)	57 (0.25)	<.001
High blood pressure	1 (0.61)	753 (3.34)	.047
Diabetes	3 (1.84)	1,036 (4.60)	.128
Dyslipidemia	0 (0)	142 (0.63)	.630

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; SCr, serum creatine; S-Cl, serum chloride; Glu, blood glucose; Hb, hemoglobin; HbA_{1c}, glycated hemoglobin; S-K, potassium; LDH, lactate dehydrogenase; S-Na, serum sodium; Plt, platelet count; T-bil, total bilirubin; WBC, white blood cell count; eGFR, estimated glomerular filtration rate (there is no normal range).

without hypersensitivity reactions had significantly higher age, AST, BUN, SCr, and LDH compared to the group with hypersensitivity reactions.

Multivariate Analysis

In univariate analysis, age, weight, outpatient status, contrast medium iodine content, AST, BUN, SCr, LDH, Plt, eGFR, history of drug allergy, asthma, and high blood pressure satisfied the criteria of $P < .05$ and proportion of missing data <50% (Table S3).

Considering multicollinearity, LDH, BUN, and eGFR were excluded on the basis of high Spearman's correlation coefficients: AST/LDH ($r = 0.51$), SCr/BUN ($r = 0.44$), and SCr/eGFR ($r = 0.55$). In addition to the above factors, sex, history of contrast

media allergy, and implementation of premedication were included as potential variables because these factors may affect the development of hypersensitivity reaction.^{11,20–22} Also, variables with missing data, such as weight, AST, SCr, and Plt, were compensated by the multiple imputation method. In addition, the interaction term was added on the basis of the hypothesis that the effect of premedication depends on the presence or absence of a history of contrast media allergy.

The results of the logistic regression analysis are shown in Table 2. The independent factors affecting the development of hypersensitivity reactions were age (odds ratio [OR], 0.98; 95% confidence interval [CI], 0.97–0.99), outpatient status (OR, 2.08; 95% CI, 1.20–3.60), contrast medium iodine content (OR, 1.02;

Table 2. Logistic Regression Analysis by Multiple Substitution Method ($n = 22,695$, Allergic Reaction 163 Cases).

Factors	Adjusted odds ratio (95% CI)	P value
Age (y)	0.98 (0.97–0.99) ^a	<.001
Body weight	1.01 (0.99–1.02) ^a	.298
Sex (male)	0.81 (0.55–1.17)	.258
Premedication	3.71 (0.77–18.0)	.103
Outpatient	2.08 (1.20–3.60)	.009
Contrast medium iodine content	1.02 (1.01–1.04) ^a	<.001
AST	1.00 (0.997–1.002) ^a	.657
SCr	0.98 (0.81–1.18) ^a	.815
Plt	1.00 (0.998–1.003) ^a	.662
Drug allergy	2.41 (1.50–3.88)	<.001
Contrast media allergy	1.66 (0.50–5.47)	.405
Asthma	17.4 (7.53–40.1)	<.001
High blood pressure	0.19 (0.03–1.37)	.099
Premedication × contrast media allergy	0.00 (0.00)	.999

AST, aspartate aminotransferase; SCr, serum creatinine; Plt, platelet count.

^aOdds ratio indicates odds per single-unit increase.

95% CI, 1.01–1.04), history of drug allergy (OR, 2.41; 95% CI, 1.50–3.88), and asthma (OR, 17.4; 95% CI, 7.53–40.1).

Sensitivity Analysis

Complete Case Analysis. In the complete case analysis, 9,102 cases with no missing data were included, and 60 cases (0.66%) developed hypersensitivity reactions. Body weight (OR, 1.02; 95% CI, 1.001–1.03), age (OR, 0.97; 95% CI, 0.96–0.99), contrast medium iodine content (OR, 1.02; 95% CI, 1.01–1.04), history of drug allergy (OR, 2.84; 95% CI, 1.50–5.40), and asthma (OR, 11.1; 95% CI, 3.06–39.9) were extracted as independent factors affecting the development of hypersensitivity reactions (Table S4).

Multivariate Analysis With Binary Classification by Cutoff Value. Receiver operating characteristic curve analysis was performed with the continuous variables to determine the cutoff value that maximizes the Youden index (Table S5). Stratification was performed above and below the cutoff value, and univariate analysis was used to compare the groups with and without hypersensitivity reactions (Table S6).

Age ≥ 68 years (OR, 0.50; 95% CI, 0.34–0.74), implementation of premedication (OR, 4.33; 95% CI, 1.01–18.5), contrast medium iodine content ≥ 25.5 g (OR, 3.07; 95% CI, 1.73–5.46), history of drug allergy (OR, 2.46; 95% CI, 1.54–3.94), and asthma (OR, 18.0; 95% CI, 7.78–41.7) were extracted as independent factors (Table S7).

Discussion

In this study, multivariate analysis with missing data compensation revealed that age, outpatient status, contrast media iodine content, history of drug allergy, and asthma are independent factors affecting the development of hypersensitivity reactions to contrast media.

This study is the first to reveal that outpatient status may be an independent factor for the development of hypersensitivity reactions to contrast media. There are two possible reasons why outpatient status might be extracted as an independent factor. First, when emergency patients receive contrast administration immediately after arrival at the hospital, they are first registered as outpatients, and thus it is possible that patients in poor general condition are disproportionately located in the outpatient setting. Second, due to their severity, these emergency outpatients cannot be interviewed by health care providers about their history of allergies, medical history, and history of adverse reactions, and consequently independent factors such as contrast media allergy history and asthma may be missed. In addition, independent factors for the development of hypersensitivity reactions to nonionic iodine contrast media were examined by compensating missing data, which has not been done in previous studies. The pattern of missing data in this study was assumed to be missing at random, and missing data were compensated by the multiple imputation method.

The validity of this study is supported by the fact that the results obtained are consistent with previous findings, as well as by the results of sensitivity analysis.

The proportions of hypersensitivity reactions were comparable to the rate of adverse reactions to nonionic iodine contrast media (0.7%–3.0%) reported in a previous study by Katayama et al.¹ Their study surveyed 198 hospitals in Japan, and our finding of a similar incidence of hypersensitivity in our single-center study supports the validity of our results. However, they did not focus on hypersensitivity in their analysis, and we believe that our study adds value in this respect.

The extracted independent factors of histories of drug allergy and asthma have already been reported to affect the development of side effects in previous studies,^{11,22} and may be universal. However, it is important to note that asthma predisposes patients to contrast-induced hypersensitivity reactions only in cases with acute symptoms.²³ Although the mechanism of development of hypersensitivity reactions is not fully understood, it is considered that immunoglobulin E (IgE) is at least partly involved. Therefore, there is a possibility that IgE-mediated sensitization increases the risk, and this could explain why asthma is an independent factor for allergic reactions to contrast media.^{12,24} Asthma is also an independent factor for

anaphylaxis, and may increase the risk of allergic reactions to contrast media, especially in patients with poorly controlled asthma.²⁵ As regards history of drug allergy, it will be necessary to investigate whether the risk varies according to the causative drug in the future.

Regarding age and contrast media iodine content, previous studies conducted in Japan showed a trend consistent with the results of this study, since age <50 years and total contrast media dose >65 g were extracted as risk factors for the development of adverse reactions.¹¹ It should be noted that this is the first study to examine the effect of iodine content on the development of hypersensitivity reactions, since the analysis in this study was performed using the amount of iodine contained in the drug rather than the total dose of contrast media. However, two reviews have stated that contrast medium iodine content is not associated with hypersensitivity reactions,^{7,26} and thus further examination is needed. On the other hand, “history of allergy to contrast media,” which is reported to be a risk factor for the development of adverse effects to contrast media, was not extracted here. A possible reason for this is that the data used in the study included only the first administrations of contrast media at the Keiyu Hospital, and thus allergy-like reactions that may have occurred previously in other hospitals may have been missed. Also, allergy to contrast media is more likely to occur after the second administration. Thus, there could have been patient background bias, since patients with a history of contrast agent allergy were excluded from the analysis, and they were more likely to be patients who received a contrast agent for a second or subsequent time.

A complete case analysis was performed as a sensitivity analysis. In this analysis, age, body weight, contrast iodine content, history of drug allergy, and asthma were extracted as factors, in good agreement with the results of logistic regression analysis with multiple imputation. In the complete analysis, outpatient status was not extracted as an independent factor. The reason for this may be related to the proportion of missing data for outpatients. In the complete case analysis, outpatients accounted for 62.5% (5,693/9,102 cases), and in the data after multiple imputations, outpatients accounted for 81.5% (18,507/22,685 cases). Outpatients often have missing laboratory data, and the complete case analysis might therefore fail to identify significant differences.

In the multivariate analysis using binary classification, there were statistically significant differences in age ≥ 68 years, implementation of premedication, contrast media iodine content ≥ 25.5 g, history of drug allergy, and asthma. Since the results were similar to those of the analysis using continuous variables, the present analysis method appears to produce reasonable results.

An important aspect of the interpretation of our findings is the magnitude of the OR in logistic regression analysis. We found that histories of drug allergy and asthma not only have high ORs (2.41 and 17.4, respectively), but also have a plausible biological mechanism, that is, IgE-mediated sensitization.^{12,24} However, there is no biological basis to support the idea that outpatients are at risk for hypersensitivity, and the OR, though significant, was not high. Further, although age and contrast medium iodine content were additionally identified as significant factors, their ORs were also low (Table 2 and Table S4), even when binary classification was employed (Table S6). Thus, these three risk factors, while they have statistical validity, remain of questionable importance due to their small ORs and/or lack of a plausible biological explanation. Furthermore, their clinical importance is reduced by the lack of available prophylactic actions.

The limitations of this study include the following: First, this study used data from a single facility, which means that the external validity of the results is not verified. Second, this study was unable to incorporate items with a proportion of missing data >50% into the analysis, so these items were not evaluated. Third, the severity in acute adverse drug reactions was analyzed collectively, so we could not evaluate differences in severity. Fourth, some factors potentially affecting the occurrence of hypersensitivity, such as history of allergic rhinitis, which involves IgE, were not evaluated.

Conclusion

In this study, age, contrast iodine content, outpatient status, history of drug allergy, and asthma were identified as independent factors affecting contrast media–induced hypersensitivity reactions. Of these, history of drug allergy and asthma are considered clinically significant due to their high ORs and plausible biological mechanisms, but the other three factors require further validation.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding Information

This work was supported by JST, CREST Grant Number JPMJCR22N1.

Data Availability Statement

Our data that support the results of this study available from the corresponding author on reasonable request.

Author Contributions

Ryouichi Chatani: conceptualization, methodology, formal analysis, investigation, and writing—original draft. Sakura Kondo: conceptualization, methodology, formal analysis, and writing—original draft. Tadamasa Kamimura: conceptualization, methodology, investigation, and writing—review and editing. Shinya Suzuki: conceptualization, investigation, writing—review and editing, and supervision. Eriko Komatsubara: investigation, data curation, and writing—review and editing. Seiichi Hayashi: investigation, data curation, and writing—review and editing. Masayuki Hashiguchi: methodology and writing—review and editing. Hayato Kizaki: methodology and writing—review and editing. Shungo Imai: methodology, validation, and writing—original draft. Satoko Hori: conceptualization, methodology, writing—review and editing, supervision, and funding acquisition.

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Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.