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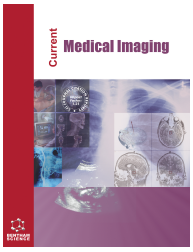

RESEARCH ARTICLE

Hypersensitivity Reactions Induced by Iodinated Contrast Media in Radiological Diagnosis: A Disproportionality Analysis Based on the FAERS Database

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Abstract:

Purpose:

This study aimed to evaluate the Pharmacovigilance (PV) and severity of hypersensitivity reactions induced by non-ionic Iodinated Contrast Media (ICM) in the radiology diagnosis reported to the United States Food and Drug Administration Adverse Event Reporting System (FAERS).

Methods:

We retrospectively reviewed the reports of ICM-induced hypersensitivity reactions submitted to the FAERS database between January 2015 and January 2023 and conducted a disproportionality analysis. The seven most common non-ionic ICM, including iohexol, iopamidol, ioversol, iopromide, iomeprol, iobitridol, and iodixanol, were chiefly analyzed. Our primary endpoint was the PV of non-ionic ICM-induced total hypersensitivity events. STATA 17.0 MP was used for statistical analysis.

Results:

In total, 35357 reports of adverse reaction events in radiology diagnosis were retrieved from the FAERS database. Among them, 6181 reports were on hypersensitivity reaction events (mean age: 57.1 ± 17.8 years). The hypersensitivity reaction-related PV signal was detected for iohexol, ioversol, iopromide, iomeprol, iobitridol, and iodixanol, but not for iopamidol. The proportion of iomeprol-induced hypersensitivity reactions and the probability of ioversol-induced severe hypersensitivity reactions have been found to be significantly increased.

Conclusion:

The probability and severity of hypersensitivity reaction events in non-ionic ICM are different. Iohexol, ioversol, iopromide, iomeprol, iobitridol, and iodixanol have higher risks compared to iopamidol. In addition, the constituent ratio of hypersensitivity reactions induced by iomeprol is significantly increased, and the associated probability induced by ioversol is significantly increased.

Keywords: Hypersensitivity reactions, Iodinated contrast media, Disproportionality analysis, Food and drug administration adverse event reporting system, Radiology, FAERS.

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1. INTRODUCTION

In the radiology diagnosis field, Iodinated Contrast Media (ICM) are an indispensable tool for improving the clarity and accuracy of diagnostic imaging [1]. ICM include ionic and non-ionic preparations. Compared to ionic ICM, non-ionic ICM have lower osmotic pressure, so their effect on blood osmotic pressure is less, and side effects are relatively less [2]. Non-ionic ICM-induced adverse reactions are relatively rare, and the associated symptoms are usually mild, but adverse reactions may still occur [3, 4]. According to the World Health Organization's report, ICM are globally used more than 75 million times a year [5]. Considering the wide usage of ICM, the probability of ICM-induced adverse reactions, especially severe hypersensitivity, is increasing, which may be fatal [4, 6]. The prevalence of ICM-induced hypersensitivity is approximately 1:170000, accounting for approximately 0.05% -0.1% of all ICM-receiving patients [3, 7]. Hypersensitivity reactions may occur as immediate hypersensitivity reactions

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within 6 hours after ICM administration or as non-immediate hypersensitivity reactions occurring more than 6 hours to several days after ICM administration [8, 9]. The frequency of immediate and non-immediate hypersensitivity reactions in non-ionic ICM-receiving patients is approximately 0.5%–3% [10, 11].

Immediate hypersensitivity reactions usually include skin reactions, respiratory reactions, circulatory system and digestive tract reactions, vascular bundle reactions, *etc*. Immediate hypersensitivity reactions can rarely become severe. Anaphylactic shock is considered the most severe type of immediate hypersensitivity reaction, marked by sudden and severe symptoms, including a rapid drop in blood pressure, difficulty breathing, cardiac complications, and loss of consciousness. Timely identification and decisive treatment are required to prevent fatal consequences of immediate hypersensitivity reactions [9, 14]. Non-immediate hypersensitivity reactions are relatively rare, and usually show urticaria, angioedema, and kidney and thyroid reactions, among others [12 - 14]. Angioedema may be caused by drugs directly affecting the vascular wall function, which results in abnormal permeability of the wall and fluid exudation in the tissue space [9, 11]. Severe Cutaneous Adverse Reactions (SCARs) are a series of severe skin symptoms caused by T cell-mediated cellular immune responses [13, 14].

The safety of ICM, which are widely used, needs to be comprehensively evaluated. Variations have been reported in the probability and severity of hypersensitivity associated with different ICM types, which suggests that their immunogenicity and sensitization characteristics differ [15]. Therefore, understanding these nuances and the aforementioned differences accurately is essential to enhance the risk-benefit model of ICM, ensure patient safety, and optimize clinical practice [16]. However, the literature on the subject is still limited, especially in large-scale practical environments.

The Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) is among the largest Pharmacovigilance (PV) databases worldwide [17]. PV is a scientific and operational domain focused on monitoring and assessing the safety of drug usage. The primary objectives of PV are identifying, evaluating, and understanding adverse drug events and other safety issues. The FAERS database, an economically efficient tool with extensive data sources, aids in effectively overcoming the limitations of expensive and time-consuming randomized controlled trials. It thus serves as a crucial complement for detecting new drugs or rare adverse reactions [18]. Some recent studies have investigated ICM-induced hypersensitivity by using a public database, comparing the probability and manifestation of adverse reactions induced by the most common ICM types [19, 20]. However, the potential differences in the probability and severity of hypersensitivity reactions among different ICM types are still unclear. The literature on the subject probability and severity of hypersensitivity in different types of ICM is still limited, especially in large-scale practical environments. It is imperative to delve into the variations among various types of severe hypersensitivity reactions associated with ICM through disproportionality analysis. Equally vital is the provision of clinical practice insights and the enhancement of patient safety in radiological diagnostic procedures. Therefore, this study used the FAERS database to evaluate the PV and severity of non-ionic ICM-induced hypersensitivity reactions in the radiology diagnosis.

2. MATERIALS AND METHODS

2.1. Data Sources and Research Design

FAERS is a publicly anonymous database, and therefore, there was no need for informed consent and approval by the agency review committee. All information can be downloaded for free from FAERS's website (https://open.fda.gov/data/downloads/). Any personal or sensitive information on this database has been appropriately de-identified to maintain confidentiality and privacy. The demographic characteristics, drugs, indications, adverse events, and other information of suspected cases are recorded in this database. Adverse events are described by the preferred term of the Medical Dictionary of Regulatory Activities (MedDRA) (version 24.0). We have, herein, analyzed the reports of ICM-related hypersensitivity reactions in the radiology diagnosis submitted to the FAERS database from January 2015 to January 2023, with each suspected drug adverse event recorded separately. After the preliminary analysis, we deleted repeated reports, missing drug reports, or adverse reactions in turn. Because of reliability limitations in certain information within the FAERS database, including report types, drug dosages, and duration of drug administration, a comparative drug analysis was not conducted based on these factors.

2.2. Information on Drugs and Adverse Reaction Events of Interest

In this study, we have identified seven common non-ionic ICM approved by the FDA from the FAERS database, namely iohexol, iopamidol, ioversol, iopromide, iomeprol, iobitridol, and iodixanol. Based on MedDRA version 24.0 criteria and allergy symptoms, the main hypersensitivity reaction events investigated (Table **S1**) were defined as angioedema, SCARs, or anaphylactic/anaphylactoid shock conditions. Terms classified under hypersensitivity or anaphylactic reactions, but not falling within the aforementioned three categories, were classified as "other anaphylactic reactions" [20]. Our primary endpoint was the PV of non-iconic ICM-induced total hypersensitivity events, and the secondary endpoint was the PV of angioedema, SCARs, anaphylactic shock, and other anaphylactic reactions. Additionally, serious adverse events in the FAERS database have been defined as meeting any of the following criteria: death, life-threatening medical conditions, caused/prolonged hospitalization, disabling/incapacitating, congenital anomaly/ birth defect, and other medically crucial conditions. Otherwise, the case is not considered serious.

2.3. Disproportionality Analysis

In the FAERS database, disproportionality analysis is often used to detect potential risk signals. We here used the Proportional Reporting Ratio (PRR), Reporting Odds Ratio (ROR), and Information Component (IC) as statistical indicators for analyzing the correlation between specific drugs

and adverse events [21 - 23]. Their calculation formula is presented in Table **S2** [24]. When any of the following conditions were met, the PV signal was considered to be detected [25]: (1) number of cases ≥ 3, PRR ≥ 2, and chi-square analysis (χ^2) ≥ 4; (2) lower limit of 95% Confidence Interval (CI) of ROR > 1; and (3) IC_{025} > 0.

2.4. Statistical Analysis

All statistical analyses were carried out using the Stata 17.0 MP software. The normality of all continuous variables was tested and expressed as mean ± standard deviation if it conformed to the normal distribution; otherwise, it has been expressed as median and quartile spacing. Classification variables have been represented by frequency and percentage. By performing the logistic regression analysis, we compared the proportion of hypersensitivity and the probability of severe hypersensitivity caused by different ICM types. A *p*-value < 0.05 indicated a statistically significant difference.

3. RESULTS

3.1. Statistical Description

In this study, 35357 reports of adverse reaction events in the field of radiology were retrieved from the FAERS database. Of these reports, 6181 described hypersensitivity reaction events (mean age: 57.1 ± 17.8 years). Table **1** lists the characteristics of hypersensitivity reaction reports in the database. Most hypersensitivity reaction reports have been found to have originated from the USA (30.0%), followed by France (24.6%), with more females (47.5%) than males (34.3%). In the reports, the most common hypersensitivity reaction event described was SCARs (56.4%, mean age: 57.1 ± 18.0 years), followed by anaphylactic/anaphylactoid shock conditions (23.8%, mean age: 58.1 ± 17.9 years) and angioedema (17.4%, mean age: 55.7 ± 16.9 years). Of all the hypersensitivity reaction reports, a total of 4424 (71.6%) were related to the seven identified ICM. The most common ICM was iohexol (29.6%), followed by iopromide (19.4%) and ioversol (18.3%).

3.2. Disproportionality Analysis

A disproportionality analysis was conducted on the eligible hypersensitivity reaction reports related to the seven identified ICM retrieved from the FAERS database (Table **2**). The total hypersensitivity reaction-related PV signals were detected in iohexol, ioversol, iopromide, iomeprol, iobitridol, and iodixanol. Of these ICM, iomeprol (PRR = 2.75, 95% CI: 2.55–2.96; χ^2 = 506.59; ROR = 4.23, 95% CI: 3.69–4.85; IC = 1.39, IC_{025} = 1.23, IC_{975} = 1.51) had the highest PRR, ROR, and IC values. However, no PV signal was detected for iopamidol (PRR = 0.97, 95% CI: 0.89–1.06; χ^2 = 0.44; ROR = 0.96, 95% CI: 0.86-1.07; IC = −0.04, IC_{025} = −0.20, IC_{975} = 0.08) and it had the lowest PRR, ROR, and IC values. These results have suggested iohexol, ioversol, iopromide, iomeprol, iobitridol, and iodixanol to be associated with a higher risk of hypersensitivity reaction than iopamidol.

Table 1. Comparison of baseline characteristics of hypersensitivity reactions induced by iodinated contrast media.

Characteristic	Hypersensitive Reaction Events	Angioedema	SCARs	Anaphylactic/Anaphylactoid Shock Conditions	Other Hypersensitivity Events
Total (n)	6181	1074	3484	1472	151
Age (mean ± SD, years)	57.1 ± 17.8	55.7 ± 16.9	57.1 ± 18.0	58.1 ± 17.9	56.5 ± 13.9
Sex	-	-	-	-	-
Female	2935(47.5)	546(50.8)	1548(44.4)	751(51.0)	90(59.6)
Male	2118(34.3)	390(36.3)	1159(33.3)	535(36.3)	34(22.5)
Unknown	1128(18.3)	138(12.8)	777(22.3)	186(12.6)	27(17.9)
Reporter country(%)	-	-	-	-	-
USA	1855(30.0)	199(18.5)	1222(35.1)	410(27.9)	24(15.9)
France	1518(24.6)	185(17.2)	1059(30.4)	232(15.8)	42(27.8)
Other countries	2808(45.4)	690(64.2)	1203(34.5)	830(56.4)	85(56.3)
Seriousness (%)	-	-	-	-	-
Serious	5298(85.7)	976(90.9)	2857(82.0)	1326(90.1)	139(92.1)
Not serious	883(14.3)	98(9.1)	627(18.0)	146(9.9)	12(7.9)

Abbreviations: SCARs = Severe cutaneous adverse reactions; SD = Standard deviation.

Table 2. Disproportionality analysis of hypersensitivity reactions induced by iodinated contrast media in radiological diagnosis.

ICM	Hypersensitive Reaction Events	A	B	C	D	PRR(95% CI)	χ^2	ROR(95% CI)	IC	IC_{025}	IC_{975}
Iohexol	Total hypersensitive events	1311	4870	4031	25145	1.51(1.43,1.60)	217.41	1.68(1.57,1.80)	0.49	0.40	0.56
	Angioedema	239	5942	5103	24073	0.23(0.20,0.26)	738.09	0.19(0.17,0.22)	-1.96	-2.18	-1.81
	SCARs	716	5465	4626	24550	0.74(0.68,0.79)	72.56	0.70(0.64,0.76)	-0.38	-0.51	-0.29
	Anaphylactic/Anaphylactoid shock conditions	326	5855	5016	24160	0.31(0.28,0.35)	564.84	0.27(0.24,0.30)	-1.52	-1.70	-1.38
	Other hypersensitivity events	30	6151	5312	23864	0.03(0.02,0.04)	1248.86	0.02(0.02,0.03)	-4.94	-5.55	-4.51

(Table 2) contd.....

ICM	Hypersensitive Reaction Events	A	B	C	D	PRR(95% CI)	χ^2	ROR(95% CI)	IC	IC_{025}	IC_{975}
Iopamidol	Total hypersensitive events	418	5763	2042	27134	0.97(0.89,1.06)	0.44	0.96(0.86,1.07)	-0.04	-0.20	0.08
	Angioedema	59	6122	2401	26775	0.13(0.10,0.17)	416.98	0.11(0.08,0.14)	-2.86	-3.29	-2.55
	SCARs	110	6071	2350	26826	0.24(0.20,0.29)	310.23	0.21(0.17,0.25)	-1.96	-2.28	-1.73
	Anaphylactic/Anaphylactoid shock conditions	248	5933	2212	26964	0.56(0.50,0.63)	100.38	0.51(0.45,0.58)	-0.79	-1.00	-0.64
	Other hypersensitivity events	1	6180	2459	26717	0(0,0.02)	557.53	0(0,0.01)	-8.17	-11.95	-6.48
Ioversol	Total hypersensitive events	808	5373	1833	27343	1.86(1.75,1.98)	340.20	2.24(2.05,2.45)	0.81	0.69	0.89
	Angioedema	183	5998	2458	26718	0.38(0.33,0.44)	220.32	0.33(0.28,0.39)	-1.33	-1.58	-1.16
	SCARs	431	5750	2210	26966	0.93(0.85,1.02)	2.67	0.91(0.82,1.02)	-0.10	-0.26	0.02
	Anaphylactic/Anaphylactoid shock conditions	158	6023	2483	26693	0.32(0.28,0.38)	261.62	0.28(0.24,0.33)	-1.54	-1.81	-1.35
	Other hypersensitivity events	36	6145	2605	26571	0.07(0.05,0.10)	514.05	0.06(0.04,0.08)	-3.66	-4.22	-3.27
Iopromide	Total hypersensitive events	860	5321	2436	26740	1.57(1.48,1.67)	186.82	1.77(1.63,1.93)	0.58	0.46	0.66
	Angioedema	221	5960	3075	26101	0.36(0.32,0.41)	292.63	0.31(0.27,0.36)	-1.38	-1.60	-1.22
	SCARs	419	5762	2877	26299	0.71(0.64,0.78)	57.31	0.66(0.60,0.74)	-0.46	-0.62	-0.34
	Anaphylactic/Anaphylactoid shock conditions	201	5980	3095	26081	0.33(0.29,0.37)	326.51	0.28(0.24,0.33)	-1.52	-1.75	-1.35
	Other hypersensitivity events	19	6162	3277	25899	0.03(0.02,0.05)	720.10	0.02(0.02,0.04)	-4.89	-5.66	-4.35
Iomeprol	Total hypersensitive events	403	5778	473	28703	2.75(2.55,2.96)	506.59	4.23(3.69,4.85)	1.39	1.23	1.51
	Angioedema	45	6136	831	28345	0.29(0.22,0.38)	94.89	0.25(0.19,0.34)	-1.76	-2.25	-1.40
	SCARs	274	5907	602	28574	1.83(1.65,2.02)	118.53	2.20(1.90,2.55)	0.84	0.64	0.98
	Anaphylactic/Anaphylactoid shock conditions	73	6108	803	28373	0.47(0.38,0.59)	52.11	0.42(-.33,0.54)	-1.06	-1.45	-0.78
	Other hypersensitivity events	11	6170	865	28311	0.07(0.04,0.13)	163.94	0.06(0.03,0.11)	-3.74	-4.76	-3.04
Iobitridol	Total hypersensitive events	142	6039	309	28867	1.82(1.59,2.09)	62.10	2.20(1.80,2.68)	0.84	0.57	1.05
	Angioedema	3	6178	448	28728	0.04(0.01,0.12)	89.55	0.03(0.01,0.10)	-4.50	-6.57	-3.30
	SCARs	104	6077	347	28829	1.32(1.12,1.57)	9.85	1.42(1.14,1.77)	0.40	0.07	0.63
	Anaphylactic/Anaphylactoid shock conditions	28	6153	423	28753	0.35(0.25,0.50)	40.25	0.31(0.21,0.45)	-1.48	-2.11	-1.03
	Other hypersensitivity events	7	6174	444	28732	0.09(0.04,0.18)	80.36	0.07(0.33,0.15)	-3.40	-4.71	-2.55
Iodixanol	Total hypersensitive events	482	5699	893	28283	2.09(1.94,2.25)	306.25	2.68(2.39,3.00)	1.00	0.85	1.11
	Angioedema	89	6092	1286	27890	0.36(0.29,0.44)	120.20	0.32(0.26,0.39)	-1.43	-1.78	-1.18
	SCARs	287	5894	1088	28088	1.20(1.08,1.34)	11.40	1.26(1.10,1.44)	0.26	0.06	0.40
	Anaphylactic/Anaphylactoid shock conditions	96	6085	1279	27897	0.39(0.32,0.47)	109.34	0.34(0.28,0.42)	-1.32	-1.66	-1.08
	Other hypersensitivity events	10	6171	1365	27811	0.04(0.02,0.07)	278.39	0.03(0.02,0.06)	-4.52	-5.60	-3.79

Abbreviations: ICM = Iodinated contrast media; A = The number of reports of the drug of interest with the adverse event of interest; B = The number of reports of all other drugs with the adverse event of interest; C = The number of reports of the drug of interest with all other adverse events; D = The number of reports of all other drugs with all other adverse events; PRR = Proportional reporting ratio; CI = Confidence interval; ROR = Reporting odds ratio; IC = Information component; SCARs = Severe cutaneous adverse reactions.

Moreover, the SCAR-associated PV signals were detected for iomeprol, iobitridol, and iodixanol. Of them, iomeprol (PRR = 1.83, 95% CI: 1.65–2.02; χ^2 = 118.53; ROR = 2.20, 95% CI: 1.90–2.55; IC = 0.84, IC_{025} = 0.64, IC_{975} = 0.98) had the highest PRR, ROR, and IC values. However, no PV signal was detected for other ICM. These results suggest iomeprol, iobitridol, and iodixanol to be associated with a higher risk of SCARs than iohexol, iopamidol, ioversol, and iopromide.

3.3. Proportion of Hypersensitivity Reactions in all ICM-induced Adverse Events

Among the seven ICM-related hypersensitivity reaction reports, the proportion of iomeprol-induced hypersensitivity reactions has been found to be increased significantly, followed by that of iodixanol-induced hypersensitivity reactions. By contrast, the proportion of iopamidol-induced hypersensitivity reactions has been found to be decreased significantly. No significant difference has been noted in the proportion of hypersensitivity reactions between iohexol and iopromide (OR = 0.92, 95% CI: 0.83–1.02, p = 0.107) and between ioversol and iobitridol (OR = 0.96, 95% CI: 0.77–1.20, p = 0.705) (Table **3**).

3.4. Probability of Severe Hypersensitivity Reactions among ICM

For the seven ICM-related severe hypersensitivity reaction reports, our results have shown the outcome of events to account for 86.5% of the total reports. In addition, the probability of severe hypersensitivity reaction of ioversol was significantly increased, followed by iohexol and iodixanol, while that for iomeprol and iobitridol was significantly decreased (Tables **4** and **5**).

4. DISCUSSION

Non-ionic ICM are widely used for radiological diagnosis, and more attention is paid to adverse reactions, especially hypersensitivity reactions. Our findings have indicated iohexol, ioversol, iopromide, iomeprol, iobitridol, and iodixanol to be associated with a higher risk of hypersensitivity reactions than iopamidol. Specifically, iomeprol has been found to be associated with the highest risk of severe skin and mucous membrane reactions. Additionally, the proportion of iomeprol-induced hypersensitivity reactions has been found to be increased significantly, whereas the probability of ioversol-

induced severe hypersensitivity reactions has also been found to be notably increased. These results emphasize the difference in the risk and severity of ICM-induced hypersensitivity reaction events among the seven ICM types. The risk of hypersensitivity reaction events must be considered when selecting contrast media and a reference must be provided for clinicians to choose drugs.

Table 3. Matrix of pairwise comparisons of the constituent ratio of hypersensitivity reactions induced by iodinated contrast media (shown as odds ratios and 95% confidence intervals).

ICM	Iohexol	Iopamidol	Ioversol	Iopromide	Iomeprol	Iobitridol	Iodixanol
Iohexol	-	-	-	-	-	-	-
Iopamidol	1.59(1.41,1.80), p < 0.001[a]	-	-	-	-	-	-
Ioversol	0.74(0.67,0.82), p < 0.001[a]	0.46(0.41,0.53), p < 0.001[a]	-	-	-	-	-
Iopromide	0.92(0.83,1.02), p = 0.107	0.58(0.51,0.66), p < 0.001[a]	1.25(1.12,1.4), p < 0.001[a]	-	-	-	-
Iomeprol	0.38(0.33,0.44), p < 0.001[a]	0.24(0.20,0.29), p < 0.001[a]	0.52(0.44,0.61), p < 0.001[a]	0.41(0.36,0.48), p < 0.001[a]	-	-	-
Iobitridol	0.71(0.58,0.87), p = 0.001[a]	0.45(0.36,0.56), p < 0.001[a]	0.96(0.77,1.20), p = 0.705	0.77(0.62,0.95), p = 0.015[a]	1.85(1.46,2.36), p < 0.001[a]	-	-
Iodixanol	0.6(0.53,0.68), p < 0.001[a]	0.38(0.33,0.44), p < 0.001[a]	0.82(0.71,0.94), p = 0.004[a]	0.65(0.57,0.75), p < 0.001[a]	1.58(1.33,1.88), p < 0.001[a]	0.85(0.68,1.07), p = 0.166	-

Abbreviation: ICM = Iodinated contrast media.

[a]$P < 0.05$ was considered to be of significant significance.

Table 4. Severity of hypersensitivity reactions caused by iodinated contrast media.

Hypersensitivity Reactions	Serious	Not Serious	Total
Iohexol	1066	245	1311
Iopamidol	385	33	418
Ioversol	618	190	808
Iopromide	797	63	860
Iomeprol	400	3	403
Iobitridol	141	1	142
Iodixanol	421	61	482
Total	3828	596	4424

Abbreviation: ICM = Iodinated contrast media.

Table 5. Matrix of pairwise comparisons of incidence of severe hypersensitivity reactions induced by iodinated contrast media (shown as odds ratios and 95% confidence intervals).

ICM	Iohexol	Iopamidol	Ioversol	Iopromide	Iomeprol	Iobitridol	Iodixanol
Iohexol	-	-	-	-	-	-	-
Iopamidol	2.68(1.83,3.93), p < 0.001	-	-	-	-	-	-
Ioversol	0.75(0.60,0.93), p = 0.008	0.28(0.19,0.41), p < 0.001	-	-	-	-	-
Iopromide	2.91(2.17,3.89), p < 0.001	1.08(0.70,1.68), p = 0.717	3.89(2.87,5.27), p < 0.001	-	-	-	-
Iomeprol	30.64(9.76,96.23), p < 0.001	11.43(3.48,37.57), p < 0.001	40.99(13.01,129.13), p < 0.001	10.54(3.29,33.77), p < 0.001	-	-	-
Iobitridol	32.41(4.51,232.79), p = 0.001	12.09(1.64,89.19), p = 0.015	43.35(6.02,311.97), p < 0.001	11.15(1.53,81.01), p = 0.017	1.06(0.11,10.25), p = 0.962	-	-
Iodixanol	1.59(1.17,2.15), p = 0.003	0.59(0.38,0.92), p = 0.021	2.12(1.55,2.90), p < 0.001	0.55(0.38,0.79), p = 0.001	0.05(0.02,0.17), p < 0.001	0.05(0.01,0.36), p = 0.001	-

Abbreviation: ICM = Iodinated contrast media.

[a]$P < 0.05$ was considered to be of significant significance.

Firstly, more females than males have accounted for most reports of ICM-related hypersensitivity reaction events, consistent with previous studies [20]. The sex-related difference in the prevalence of allergic diseases may be due to genetic factors related to the X chromosome, epigenetic changes, sex hormones, and drug exposure [26]. Second, on analyzing the seven non-ionic ICM, we have noted iohexol, ioversol, iopromide, iomeprol, iobitridol, and iodixanol to be associated with a higher risk of hypersensitivity reactions than iopamidol. Moreover, iomeprol, iobitridol, and iodixanol have been reported to be associated with a higher risk of severe SCARs than other ICM. This may indicate that when selecting ICM, doctors and patients must focus on the risk of hypersensitivity reactions caused by most drugs, especially the high risk of SCARs associated with the use of iomeprol, iobitridol, and iodixanol. Among them, the PRR (2.75, 95 CI%: 2.55–2.96) and ROR (4.23, 95 CI%: 3.69–4.85) of iomeprol were the highest, and iomeprol was responsible for the largest proportion of hypersensitivity reactions, being consistent with the results of previous analyses [19, 20]. This finding highlights the relatively high risk of iomeprol-induced hypersensitivity reactions. According to Cha *et al*., iomeprol and iobitridol significantly increased the probability of hypersensitivity reactions, whereas iohexol and iopromide significantly decreased the probability [27]. Kim's study [15] has also unveiled iomeprol-induced immediate hypersensitivity reactions to be more frequent than iobitridol-, iopamidol-, and iohexol-induced immediate hypersensitivity reactions. This may be related to the relatively low osmotic pressure and chemical structure of iomeprol. Additionally, some studies have speculated that iomeprol exerts hemodynamic effects. After low osmotic iodide was administered under general anesthesia, blood pressure was found to be decreased significantly and heart rate increased for a brief period [19, 28]. The effect of iomeprol on patients with heart diseases needs to be further evaluated.

However, some previous studies [29, 30] have employed case studies to study ICM-related SCARs. These studies have reported the most common SCAR-causing ICM to be iomeprol, iohexol, and iodixanol, different from our results. SCAR signals of iobitridol have been detected, and not SCAR signals of iohexol. This inconsistency may be a result of the limited sample size, diversity, and follow-up time of case systems or randomized controlled trials, and insufficient data for predicting real clinical drug use. Finally, the analysis has shown the probability of severe hypersensitivity reactions of ioversol to be significantly increased, followed by iohexol and iodixanol, while that of iomeprol and iobitridol to be decreased significantly. In a study [31], elevated levels of plasma histamine and trypsin were associated with the severity of ICM-induced hypersensitivity reactions in patients. However, a South Korean survey revealed no differences in the probability of moderate and severe ICM-related adverse reactions between ICM generics [2]. This inconsistency may be a result of the lack of a separate grouping analysis of ICM-associated severe hypersensitivity reactions in that study.

The risk factors for ICM-associated hypersensitivity reactions have not been completely determined. Some studies have demonstrated the history of ICM-related hypersensitivity reactions, the existence of allergic diseases, hyperthyroidism, and family histories of these reactions, which may serve as risk factors [27]. ICM-induced hypersensitivity reactions are typically categorized as immediate and non-immediate hypersensitivity reactions [10], and their underlying mechanisms remain unclear and have been speculated for many years. Several studies [32 - 34] have supported the discovery of specific IgE-mediated immune mechanisms underlying immediate hypersensitivity reactions, which may include (1) direct membrane effect that may be related to the osmotic pressure of the ICM solution, (2) activation of the complement system, and (3) direct formation of bradykinin. In addition, the mechanism underlying non-immediate hypersensitivity reactions is T cell-dependent [35, 36]. T cell activation has also been observed in peripheral blood and skin test areas. The expression of skin lymphocyte-associated antigens and other chemokine receptors and integrins interacting with their corresponding ligands have also been detected [37, 38].

5. LIMITATION

Our study involves several limitations. Firstly, the use of each ICM type, such as medication time, injection rate, injection dose, and ICM concentration, was not considered in this study. Also, the relationship of these conditions with the probability of hypersensitivity reactions remains unclear. Secondly, because this is a voluntary reporting system, patients may be more likely to submit relatively serious adverse events to the FAERS database, which may induce selection bias. In addition, the FAERS database contains incomplete or missing information and potentially repetitive information, which may affect the results' accuracy. Therefore, additional population-based studies are warranted to confirm the study results.

CONCLUSION

The probability and severity of hypersensitivity reaction events associated with non-ionic ICM have been found to be different. Iohexol, ioversol, iopromide, iomeprol, iobitridol, and iodixanol have been found to have higher risks compared to iopamidol. In addition, the constituent ratio of hypersensitivity reactions induced by iomeprol has been found to be significantly increased, as well as the associated probability induced by ioversol. Further prospective studies are needed to help select the ICM that are most suitable for patient safety.

AUTHORS' CONTRIBUTION

Jinjin Long: Primarily responsible for the overall study design, data collection, implementation of data analysis, and manuscript writing.

Yifan Ji: Participated in study design, assisted in data collection and organization, and was responsible for the selection of data analysis methods and execution of statistical analysis.

Yawen Zhang: Responsible for literature screening and data extraction.

Xinghui Li: Reviewed and revised the manuscript, and provided significant academic guidance on study design and result analysis.

LIST OF ABBREVIATIONS

PV	=	Pharmacovigilance
FAERS	=	Food and Drug Administration Adverse Event Reporting System
IC	=	Information Component

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

STROBE and SAGER guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Declared none.

SUPPLEMENTARY MATERIALS

Supplementary material is available on the Publisher's website.

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