Immediate Reactions to Iodinated Contrast Media Prevalence of IgE-mediated Hypersensitivity

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Abstract

Background

After administration of iodinated contrast media (ICM) some patients develop an immediate hypersensitivity reaction (IHR). A specific allergic IgE-mediated mechanism may be involved.

Objective

To determine the prevalence of allergic patients among ICM reactors and to evaluate the negative predictive value (NVP) of skin testing for ICM.

Methods

All patients who attended a single center for an allergy work-up between 2010 and 2019 due to a prior IHR after an ICM injection were included retrospectively. ICM allergy was diagnosed if prick tests or intradermal tests were positive. Further information concerning secondary exposure to ICM was obtained from all patients with negative skin tests to determine whether ICM re-exposure led to an IHR.

Results

Skin tests identified ICM allergy in 7 out of 85 patients (8.2%). Frequency of IgE-mediated hypersensitivity among patients increased with increasing reaction severity. The NPV of skin testing for ICM allergy was 87.8% [95%CI 75.2;95.4].

Conclusion

The low prevalence of IgE-mediated hypersensitivity among patients with IHR to ICM should not delay allergy workup. Earlier skin tests and provocation tests with skin-test negative ICM may help allergists to find a reliable alternative ICM.

Background

Routine radiographic procedures – e.g. computed tomography, angiography, intra-articular imaging – often involve the use of iodinated contrast media (ICM). These agents enhance anatomic structures by improving contrast, making it easier to identify lesions [1]. Water-soluble ICM have specific physical and chemical properties that determine their polymerization, ionicity and osmolarity. ICM are generally administered via an intravascular injection, but other routes include intra-articular and intracavitary injections and oral intake [1]. After administration, ICM remain in the extracellular space and are submitted to intravascular osmotic forces in the bloodstream. They can pass through capillary basal membranes according to the concentration gradient but do not cross the blood-brain barrier [2].

The prevalence of all-cause adverse reactions to ICM injections is currently estimated to range from 0.4% to 8% depending on the agent used [3-6]. Most practitioners prefer non-ionic ICM because adverse reactions have been less severe than with ionic ICM [7], but with no guarantee all reactions can be avoided. Hypersensitivity reactions are sometimes observed, but unpredictably [8].

A hypersensitivity reaction is defined as a reaction to a product administered at a dose considered to be non-toxic for a given individual [9,10]. It is recognized as an allergic reaction when there is proof of an underlying immunological mechanism [10]. In the past, most ICM-related hypersensitivity reactions were considered to be pseudo-allergic because manifestations are mild to moderate, dose-independent, and unpredictable [11,12]. More recently, studies have demonstrated authentic immunological mechanisms only in certain patients, notably immediate reactions mediated by

immunoglobulins-E (IgE) [13-16], or late reactions mediated by T-lymphocytes [17,18]. For these 'allergic' patients, re-exposure to ICM could raise a risk of life-threatening recurrence [10].

An immediate hypersensitivity reaction [IHR] occurs when the delay after the ICM administration is one hour or less. The severity of an IHR is generally assessed using the Ring and Messmer scale (Table 1) [19,20]. Grade I reactions are the most common. For example, in the CIRTACI study, a multiple-center prospective study of ICM-related IHR, 55.9% of the IHR were Grade I [13]. Late hypersensitivity reactions occur one hour to seven days after ICM administration [21,22] and appear to be less frequent than IHRs. In one report from Korea, after 11,712,796 ICM injections performed over the study period (2014 to 2016), there were 44,467 cases of IHR versus 5,725 late reactions [8].

Our study focused on IHR occurring after administration of ICM. For an IHR to be considered an allergic reaction, a medical history compatible with IHR is necessary, but not sufficient, to establish the diagnosis. Allery is confirmed if undiluted ICM prick test (PT) or diluted ICM intradermal skin test (IDT) is positive. In the CIRTACI study, among the 209 patients with an IHR after an ICM injection who had skin tests, allergy was diagnosed in 19.6% [13]. However, in their review of the literature, Yoon et al. [23] found that allergy has been diagnosed in 4% to 100% of patients with IHR.

The main objective of this study was to determine the prevalence of IgE-mediated IHR to ICM in patients attending our allergology department for an allergy work-up because they had experienced an IHR after exposure to ICM. The secondary objective was to study the reliability of the routine skin tests used in our allergology department.

Methods

This was a retrospective quantitative study conducted at the allergology department of the Saint-Vincent-de-Paul Hospital in Lille, part of the Catholic Institute of Lille Hospital Group (GHICL).

Study population

All consecutive patients attending the allergology department of the Saint-Vincent-de-Paul Hospital from January 2010 to June 2019 for skin tests for suspected ICM allergy were identified. To be eligible for inclusion in the study, patients had to have presented a reaction to ICM, either immediately (<1 hour) or an undetermined time (in which case an immediate reaction could not be excluded) after the injection.

Exclusion criteria were skin tests not performed in the allergology department, late reaction (>1 hour) after ICM injection, uncertainty as to whether the reaction concerned an ICM agent, and patient refusal for use of personal clinical data.

This study was approved by the GHICL Institutional Review Board (ref. CIER-2019-23). Study methodology complied with the engagements the GHICL has made to the national commission for informatics and freedom (CNIL).

Data collection

Data collected from the patient's medical file included: sex, age, medical history, treatments, allergology work-up results, history of the initial reaction to ICM with identification of the agent involved, concomitant medications, type of exploration for which the ICM was used, Ring and Messmer Grade, time from the reaction to skin testing (expressed in months).

Skin tests performed in the allergology department were done with the following ICM agents: iobitridol 300 mg/ml; iohexol 350 mg/ml; iopamidol 30 mg/ml; iopromide 300 mg/ml; ioversol 350 mg/ml; iodixanol 320 mg/ml; ioxaglate 320 mg/ml; ioxitalamate 300 mg/ml. The results of PTs using undiluted ICM agents and IDT tests using diluted (10^{-5} to 10^{-1}) ICM agents were recorded for all patients. The diagnosis of Ig-E-mediated hypersensitivity to ICM was retained for

all patients who had one positive skin test. PTs were considered positive if a wheal measuring >3 mm was observed at the 20-min reading [24]. An IDT was considered positive if the wheal diameter increased more than 3 mm at the 20-min reading [25].

All patients included in the study were contacted by phone to ascertain information about any new injection of ICM after the skin tests. In the event of re-exposure, the identity of the ICM agent, the type of exploration performed, and the administration route were recorded. If a new reaction occurred after re-exposure to the ICM, the time line and the clinical severity (Ring and Messmer Grade) were recorded, based on information provided by the patient and elements noted in the radiology file. The patient's attending physician was contacted for further information if needed.

Statistical analysis

The statistical analysis was performed with R software (version 3.4.2) by the biostatistics unit of the GHICL Clinical Research and Innovation Delegation.

A descriptive analysis was performed to answer the main objective of the study. Results are presented as number and percentage for discrete variables and mean and standard deviation for continuous variables. The 95% confidence interval (95%CI) was determined for the IgE-mediated hypersensitivity reaction. Patients were classed as allergic (IgE-mediated hypersensitivity reaction) or non-allergic (non IgE-mediated hypersensitivity reaction) for bivariate comparison using Fisher's exact test for discrete variables and the Mann-Whitney-Wilcoxon test for continuous variables. Significance level was set at 5% for all analyses.

In order to study the reliability of the skin tests, the negative predictive value (NPV) and the 95%CI of the routine allergology work-up to predict a hypersensitivity reaction to ICM was determined using as the gold standard the absence of an IHR after re-exposure to at least one ICM injection in skin test-negative patients.

Results

Study population

We identified 141 patients who attended the allergology department from January 2010 to June 2019 (Fig. 1) for skin tests. We excluded 56 of these patients because they had had a late reaction (n=30), uncertain reaction to ICM (n=16), a reaction unrelated to an ICM injection (n=8), or had not had skin tests (n=2). None of the patients decline use of their clinical data.

The study population was thus composed of 85 patients (Table 1), 33 men and 52 women. Mean patient age was 58 ± 13 years. The youngest patient included was 22 years old. The IHR was a first reaction for 74 patients (87.1%). For 11 patients, the time line of the hypersensitivity reaction after the ICM injection was uncertain. The reaction was scored Grade I for 48 patients (56.5%), Grade II for 28 (32.9%), Grade III for 9 (10.6%). There were no cases of Grade IV reaction. The iodinated agent was identified for 31 patients (36.5%): iodixanol (n=13); ioversol (n=8); iobitridol (n=4); iohexol (n=4); iomeprol (n=1); iopamidol (n=1). The agent was administered via an intravascular injection for 52 patients (75.4%) and an intra-articular injection for 13 (18.8%). Mean time from the reaction to skin testing was 111 ± 124 months, i.e. 9.3 ± 10.3 years.

Secondary exposure was recorded in 49 patients, i.e. 57.6%: 58.3% for patients whose first reaction was Grade I; 57.1% for Grade II; 55.6% for Grade III. All patients with secondary exposure had had negative skin tests for ICM during the allergology work-up. Four of the seven patients exhibiting IgE-mediated hypersensitivity to at least one ICM agent during the allergology work-up were re-exposed to an alternative ICM agent (negative skin tests).

Prevalence of IgE-mediated hypersensitivity to ICM

The prevalence of IgE-mediated hypersensitivity was 8.2% [95%CI 1.0;16.0], being observed in seven out of 85 patients. Hypersensitivity to ICM was diagnosed with a PT in one patient and a diluted IDT in six patients (Table 3). Analyzing IgE-mediated hypersensitivity as a function of the initial severity, Grade I reactions signaled hypersensitivity in 4.2% of patients (2/48), Grade II reactions in 10.7% (3/28) and Grade III reactions in 22% (2/9) (Fig. 2).

Five of the seven patients with a diagnosis of allergy to ICM reacted to one single ICM agent during the skin tests. Cross reaction was suspected in two patients between iodixanol, iohexol and ioversol and between iodixanol and ioxitalamate, respectively.

Negative predictive value

The NPV of the allergology work-up was 87.8% [75.2;95.4]. Six re-exposed patients (12.2%) had an IHR after a new administration of an ICM agent despite negative skin tests for that agent (Table 4). Reactions after secondary exposure were Grade I for one patient (16.7%), Grade II for four (66.7%), and Grade IV for one patient (16.7%). Five out of these six reactions (83.3%) were less or equally severe compared with the initial reaction. For one female patient who was re-exposed to iodixanol, the second reaction was more severe than the first one, Grade IV versus Grade III.

Discussion

In our department, the allergology work-up established the diagnosis of allergy in only one out of ten patients with a history of acute-phase reaction to ICM. This percentage is lower than found in the CIRTACI study (19.6%) and is in agreement with the results of a single-center study reported by Prieto-Garcia et al. who found IgE-mediated IHR in 11/106 patients (10.4%) [26]. These authors had a prospective cohort comparable to ours as it concerned all patients attending their allergology department for an acute-phase reaction to ICM.

Similar to data in the literature, we found that the percentages of allergic patients in the cohort increased with more severe initial reactions to ICM [13]. Most of the patients in our study who were allergic to ICM had positive skin tests for only one ICM agent [16]. This might imply that there is a different allergen for each ICM agent, although to date no such allergens have been identified [27].

Eleven of the patients included in our study population had had an initial reaction after ICM exposure, but with an uncertain chronology. This may have been a selection bias. One of these 11 patients had a diagnosis of IgE-mediated hypersensitivity. This gave a 9.1% rate of allergy in these patients, a rate that is coherent with the results for the main objective of this study.

Data on the NPV of skin tests are scarce [26,28,29]. In our study, skin tests produced a 87.8%[72.2;95.4] NPV for allergy, a rate which is lower than reported by Schrijvers et al. who found 94.2%[89.6;97.2] [29]. Our NPV may have been underestimated since it was determined using data from all patients with a second exposure, even though confirmation that the initial reaction was attributable to ICM could not be obtained in some. One of these patients had acute heart failure and experienced a Grade IV reaction (fatal cardiac arrest) one hour after an injection of iobitridol during a secondary procedure. This points out why iobitridol is contraindicated after an allergology work-up.

This study demonstrated that recurrent IHR to ICM still occur after negative skin tests in one out of 10 patients. The causes of these recurrent reactions should be examined.

First, this situation might be explained by non-IgE-mediated IHR resulting from a non-specific histamine release mechanism [30]. In this case, histamine release from mast cells would not be induced by specific IgE-antigen binding,

but by binding between a non-specific ligand and receptors on the cell surface [31]. Despite the negative skin tests and premedication with corticosteroids, certain authors have observed what they call breakthrough reactions to ICM [32,33].

Second, some reactions might occur without any relationship with the administered ICM. For instance, it is difficult to attribute the cause of a reaction to an ICM with certainty if several drugs had been administered at the same time.

Third, skin tests might lack sensitivity. According to current guidelines, skin tests are recommended two to six months after the initial reaction, such tests expected to be less sensitive after six months [5,14,34]. In their study, Brockow et al. found that 50% of patients who underwent skin tests within six months had positive tests whereas only 22% of those with skin tests later were positive [14]. On average, time from the hypersensitivity reaction to skin testing was nine years in our study. Need to undergo an exploration involving administration of an ICM appeared to be our patients' main motivation for having skin tests.

Certain authors propose re-introduction of the ICM by intravenous injection as a complementary allergology test in addition to skin tests [16,35,36]. Considered to be the gold standard for identifying drug-induced allergy, reintroduction of the ICM that does not provoke a reaction would predict that an acute reaction will not occur after re-exposure to the same agent [30,34]. At the present time, proof of this concept has not been clearly established. Some authors propose using these tests only if the patient has had a prior severe reaction to ICM [37] or if the skin test is positive for a given agent, in order to confirm the absence of reaction to an alternative ICM (negative skin test) [16]. Salas et al. used intravenous injections at increasing doses (5ml, 15 ml, 30ml, then 50ml, cumulative dose 100ml) given in one day at 45 min intervals [36]. For Morales et al. the test was given over two days. The first day the patient received intravenous injections (5ml, 30ml, 60ml, cumulative dose 95ml) administered at 30 min intervals. If there was no reaction, the second day a single 120ml dose was injected [16]. This method is controversial. Certain authors think that progressively augmented doses could induce desensitization and thus compromise the test results [38].

Besides skin tests and provocation tests, there are not many allergology tools to study acute allergy to ICM. Assay of specific IgEs has not been found reliable and few studies have been able to recognize them [39]. The physical-chemical properties of ICM would be incompatible with laboratory tests used to identify IgE [40]. The basophil activation test (BAT) is also not used as a routine test. The BAT is positive if in vitro histamine release from polymorphonuclear basophils is noted after exposure to an ICM agent [38,41]. The diagnostic values of this test are unknown. Salas et al. [35] reported five patients with a history of IHR to ICM among 90 with positive skin tests for at least on ICM agent and three patients with negative skin tests who had a positive BAT. These three patients were considered to be allergic to ICM.

Conclusions

Around 10% of patients are diagnosed allergic to ICM. Recurrent IHR to ICM still occur after negative skin tests in one out of 10 patients. Negative-skin tests patients may have severe reactions at re-exposure. Negative skin tests to ICM do not guarantee a safe re-exposure.

The low prevalence of IgE-mediated hypersensitivity in patients who have had an acute reaction to ICM should not deter allergology testing. An allergy work-up provides more than simple binary information: allergic/non-allergic. It gives insight into the appropriate management strategy for future use of ICM. Early testing for reactions to ICM and the development of intravenous reintroduction tests will enable clinicians to predict an absence of reaction to a new administration of these products.

Abbreviations

BAT basophil activation test

CNIL national commission for informatics and freedom

GHICL Catholic Institute of Lille Hospital Group

ICM iodinated contrast media

IDT intradermal skin test

IgE immunoglobulins E

IHR immediate hypersensitivity reaction

NVP negative predictive value

PT prick test

Declarations

Ethics approval and consent to participate

- All patients gave their approval.
- This study was approved by the GHICL Institutional Review Board (ref. CIER-2019-23). Study methodology complied with the engagements the GHICL has made to the national commission for informatics and freedom (CNIL).

Consent for publication

- Not applicable

Availability of data and materials

- The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

- The authors declare that they have no competing interests

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Authors' contributions

- JC wrote this article.
- MS performed allergy work up and was a major contributor in writing this article.
- SG analysed the patient data.
- TM performed allergy work up and was a major contributor in writing this article.
- CD performed allergy work up and was a major contributor in writing this article.

- All authors read and approved the final manuscript.

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Tables

Table 1. Ring and Messmer scale: severity of immediate hypersensitivity reactions

Grade	Symptoms
I	Skin, mucosal tissue: itch, flushing, urticaria, angioedema
II	Moderate multiple organ involvement. Measurable, but not life-threatening symptoms: skin and mucosal reaction, hypotension, tachycardia, respiratory disorder, cough, difficult inspiration.
III	Severe single- or multiple-organ involvement. Life-threatening symptoms: shock, tachycardia or bradycardia, arrhythmia, bronchospasm.
IV	Cardiac and/or respiratory arrest

Table 2. Patients with a history of immediate hypersensitivity reaction to iodinated contrast media (n=85): comparison between allergic and non-allergic patients

	Non-missing values n	Cohort	Allergic	Non-allergic	p
Number (%)		85	7 (8.2)	78 (91.8)	
Female, n(%)	85	52 (61.2)	4 (57.1)	48 (61.5)	1
Age (years), mean ± standard deviation, n(%)	85	58 ± 13	55 ± 7	59 ± 14	0.17
History of asthma, n(%)	79	11 (13.9)	1 (14.3)	10 (13.9)	1
History of chronic obstructive pulmonary disease, n(%)	79	4 (5.1)	0 (0)	4 (5.6)	1
History of atopic dermatitis, n(%)	79	6 (7.6)	0 (0)	6 (8.3)	1
Suspected drug allergy, n(%)	82	36 (43.9)	2 (28.6)	34 (45.3)	0.46
History of cardiovascular disease (smoking excluded) , n(%) tabac)	81	53 (65.4)	3 (42.9)	50 (67.6)	0.23
Active smoker or cessation less than 3 years, n(%)	53	17 (32.1)	1 (25)	16 (32.7)	1
History of cancer, n(%)	79	25 (31.6)	3 (42.9)	22 (30.6)	0.67
History of chronic kidney failure, n(%)	79	3 (3.8)	1 (14.3)	2 (2.8)	0.25
Family history of atopic dermatitis, n(%)	33	2 (6.1)	0 (0)	2 (6.5)	1
Family history of allergic rhinitis, n(%)	80	7 (8.8)	1 (14.3)	6 (8.2)	0.49
Treatment with conversion enzyme inhibitor, n(%)	77	14 (18.2)	0 (0)	14 (20)	0.34
Treatment with angiotensin II receptor blocker, n(%)	77	16 (20.8)	1 (14.3)	15 (21.4)	1
Treatment with beta blocker, n(%)	78	23 (29.5)	1 (14.3)	22 (31)	0.67
Iodinated contrast medium involved	85				0.82
- Iobitridol, n(%)		4 (4.7)	0 (0)	4 (5.1)	
- Iodixanol, n(%)		13 (15.3)	0 (0)	13 (16.7)	
- Iohexol, n(%)		4 (4.7)	0 (0)	4 (5.1)	
- Iomeprol, n(%)		1 (1.2)	0 (0)	1 (1.3)	
- Iopamidol, n(%)		1 (1.2)	0 (0)	1 (1.3)	
- Iopromide, n(%)		0 (0)	0 (0)	0 (0)	
- Ioversol, n(%)		8 (9.4)	1 (14.3)	7 (9)	

- Ioxaglate, n(%)		0 (0)	0 (0)	0 (0)	
- Ioxitalamate, n(%)		0 (0)	0 (0)	0 (0)	
- Unknown, n(%)		54 (63.5)	6 (85.7)	48 (61.5)	
Type of exploration	69				0.45
- Computed tomography arthrography, n(%)		4 (5.8)	0 (0)	4 (6.2)	
- Cholecystography, n(%)		1 (1.5)	1 (20)	0 (0)	
- Computed tomography colonography, n(%)		2 (2.9)	0 (0)	2 (3.1)	
- Coronarography, n(%)		4 (5.8)	0 (0)	4 (6.2)	
- Coronary computed tomography, n(%)		1 (1.5)	0 (0)	1 (1.6)	
- Hysterography, n(%)		2 (2,9)	0 (0)	2 (3,1)	
- Intra-articular injection: spine/knee, n(%)		9 (13)	0 (0)	9 (14,1)	
- Computed tomography (other than spine)		40 (60)	4 (80)	36 (56,2)	
- Computed tomography (spine), n(%)		2 (2,9)	0 (0)	2 (3,1)	
- Urography, n(%)		4 (5,8)	0 (0)	4 (6,2)	
Administration route	69				0.28
- Intravascular, n(%)		52 (75.4)	4 (80)	48 (75)	
- Intra-articular, n(%)		13 (18.8)	0 (0)	13 (20.3)	
- Intracavitary, n(%)		3 (4.3)	1 (20)	2 (3.1)	
- Oral, n(%)		0 (0)	0 (0)	0 (0)	
- Intravenous + oral, n(%)		1 (1.5)	0 (0)	1 (1.6)	
Ring and Messmer Grade	85				0,14
- I, n(%)		48 (56.5)	2 (28,6)	46 (59)	
- II, n(%)		28 (32.9)	3 (42.9)	25 (32.1)	
- III, n(%)		9 (10.6)	2 (28,6)	7 (9)	
- IV, n(%)		0 (0)	0 (0)	0 (0)	
Chronology of initial reaction	85				
- Uncertain, n(%)		11 (12.9)	1 (14.3)	10 (12.8)	1
Time from reaction to skin tests (months), mean ± SD	71	111 ± 124	225 ± 166	100 ± 116	0.08

Table 3. Skin test results in patients allergic to iodinated contrast media (ICM).

Sex	Age (years)	Chronology of initial reaction	ICM at initial reaction	Exploration	ICM administration route	Grade	Time from initial reaction to skin tests (months)	Positive skin test(s)
Female	55	Immediate	Unknown	Scanner	Intravenous	I	240	IDT 10^{-5} iobitridol
Male	60	Immediate	Unknown	Scanner	Intravenous	II	60	IDT 10^{-1} iopromide
Female	51	Immediate	Ioversol	Scanner	Intravenous	III	6	IDT 10^{-1} iodixanol iohexol ioversol
Female	49	Immediate	Unknown	Scanner	Intravenous	III	360	PT iopamidol
Male	46	Immediate	Unknow	Unknown	NR Unknown	II	252	IDT 10^{-4} iodixanol ioxitalamate
Male	57	Uncertain	Ioversol	Scanner	Intravenous	I	NR	IDT 10^{-2} iopromide
Female	66	Immediate	Unknown	Cholecys-tographie	Intra-cavity	II	432	IDT 10^{-1} iohexol

IDT = intradermal skin test

Table 4. Patients who had an acute reaction after re-exposure to iodinated contrast media (ICM) after skin tests.

Sex	Age at skin tests (years)	ICM administration route	Grade	Time from initial reaction to skin tests (months)	Skin tests	Year of skin tests	ICM reintroduced (administration route)	Grade
Male	66	Unknown (IA)	II	60	Negative	2016	Iohexol (IA)	II
Female	51	Ioversol (IV)	III	6	Positive IDT Iodixanol Iohexol Ioversol	2017	Iopamidol (IV)	II
Male	72	Ioversol (IV)	II	5	Negative	2017	Iohexol (IV)	II
Female	69	Iodixanol (IV)	III	11	Negative	2018	Iodixanol (IV)	IV
Male	58	Iodixanol (IV)	I	72	Negative	2018	Iohexol (IV)	I
Female	52	Iopamidol (IA)	II	132	Negative	2016	Iodixanol (IA)	II

IDR = intradermal reaction ; IV = Intravenous ; IA = Intra-articular

Figures

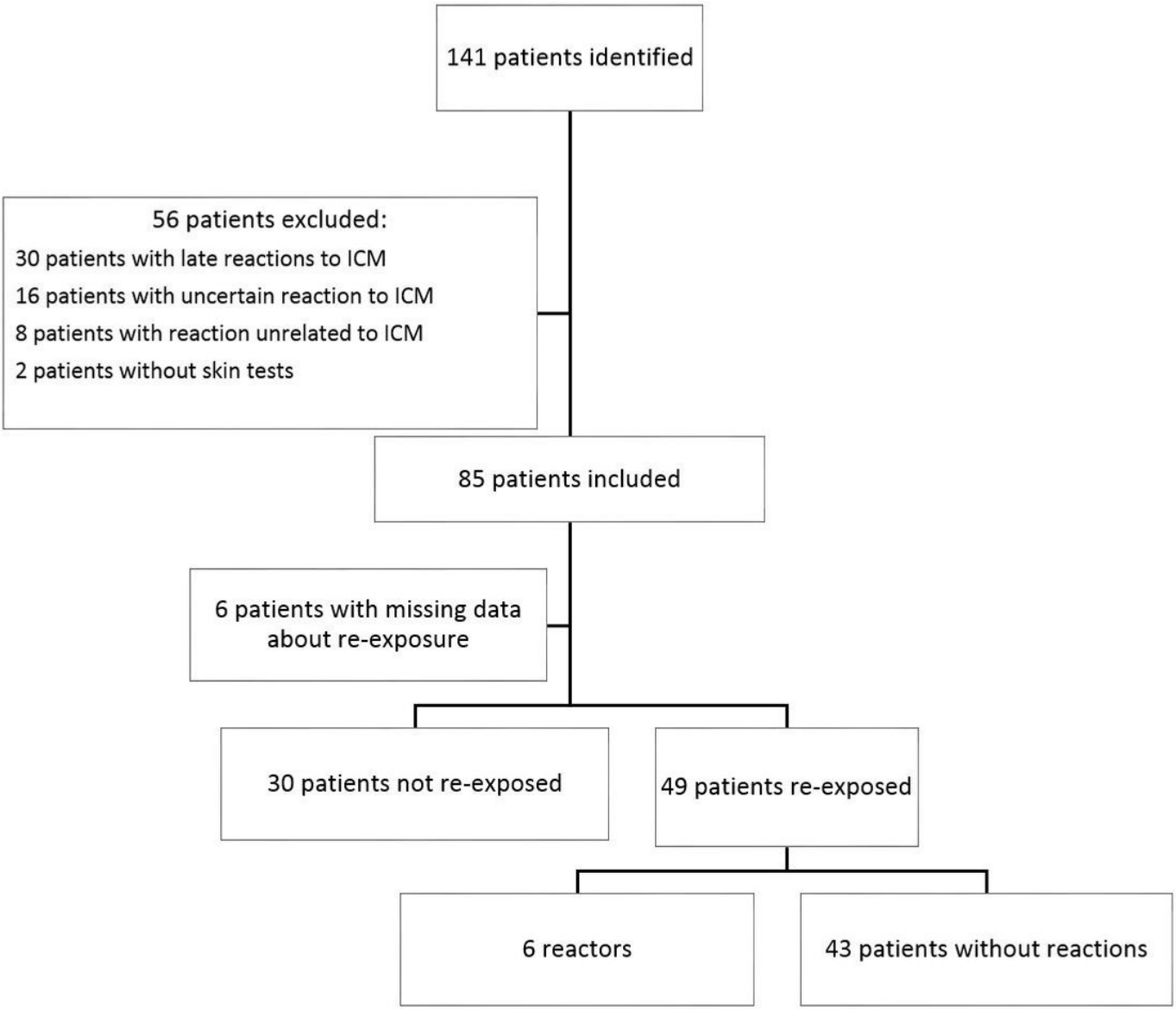

Figure 1

Flow chart

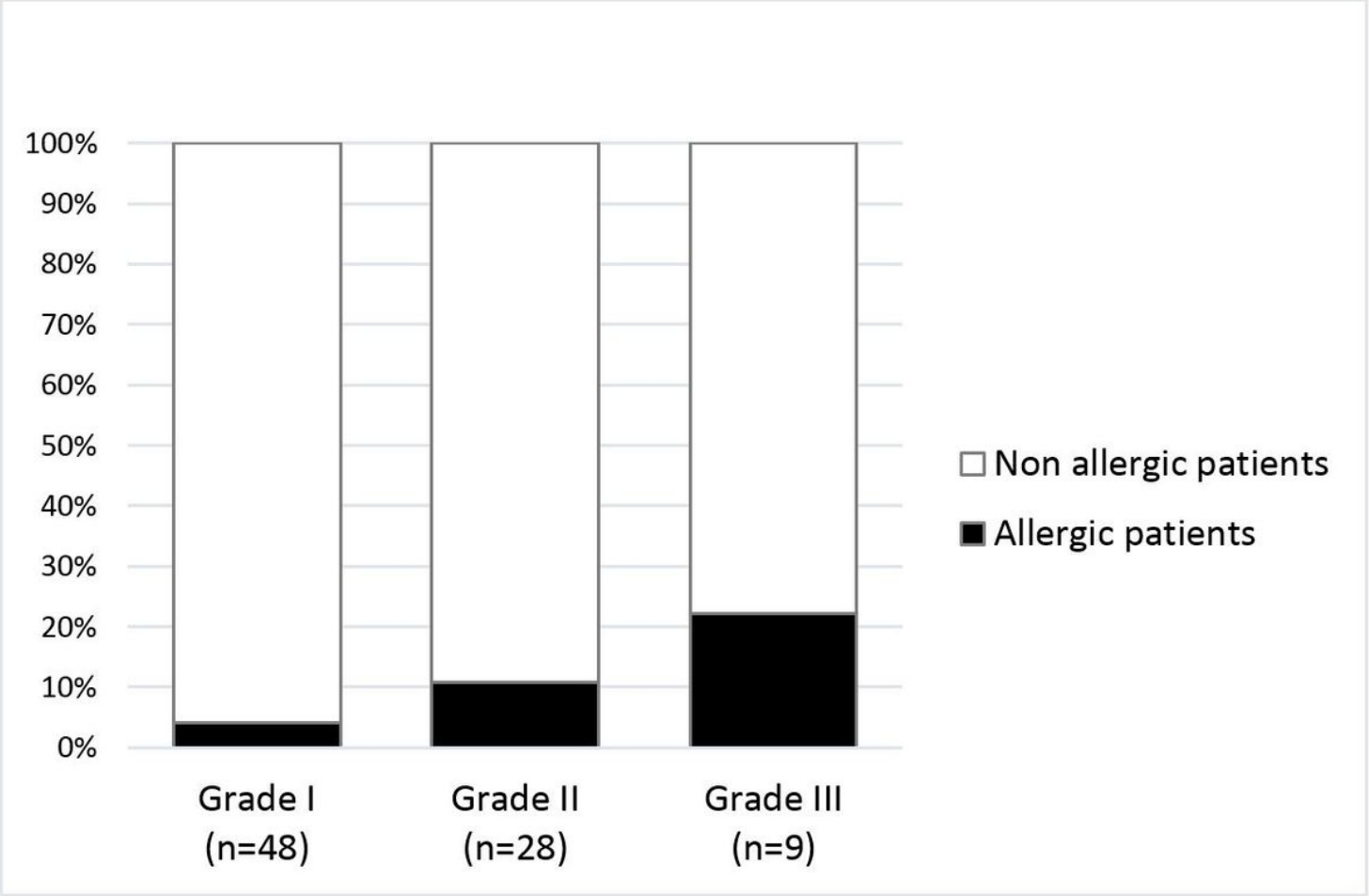

Figure 2

Proportion of patients allergic to iodinated contrast media by clinical grades