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Hypersensitivity reactions to iodinated radiocontrast media: Cluster analysis reveals distinct clinical phenotypes

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ABSTRACT

Background: Drug hypersensitivity reaction (DHR) to iodinated radiocontrast media (iRCM) is reported in 1%–3% of injections. Risk assessment of patients with suspicion of DHR to iRCM relies solely on clinical phenotyping and drug allergy workup. Using a novel unsupervised TwoStep cluster analysis, we aimed to identify prototypic patterns within a large cohort of patients evaluated for a potential iRCM DHR.

Methods: A retrospective study was conducted using data from the Drug Allergy and Hypersensitivity Database of the Allergy Unit, University Hospital of Montpellier, Montpellier, France. All referred patients during February 2001 to December 2019 with suspicion of iRCM DHR with either confirmed positive or confirmed negative skin tests were included in the analysis.

Results: A total of 1439 patients were evaluated. The chronology of the index reaction was immediate and nonimmediate in 77.1% and 22.4%, respectively. Cluster analysis categorized the total study population in 5 clusters. Cluster 1 compiled all nonimmediate and cluster 2–5 almost all immediate reactors. Cluster 1 and 2 had recent reactions (<1 y) with mostly known iRCMs and the highest iRCM allergy prevalence (16–17%). In the other clusters, more remote reactions, unknown iRCMs and a lower allergy prevalence (3–8%) was observed. Chronology and semiology of the index reaction were the factors most strongly differentiated among clusters. History of anaphylactic shock and chronology of immediate hypersensitivity reactions were shown to be independent predictors of allergy with adjusted OR (aOR) of 4.68 (95%CI: 3.01–7.27, $p < 0.001$) and 2.51 (95%CI: 1.67–3.78, $p < 0.001$), respectively.

Conclusions: Unsupervised cluster analysis identified 5 prototypic patterns within patients with a suspected DHR to iRCMs. Well-phenotyped patients cluster together in 2 groups in which the prevalence of allergy is approximately 1 in 6. However, this value decreases for patients with reactions dating back to more than a decade.

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INTRODUCTION

Iodinated radiocontrast media (iRCM) is used to enhance the visibility of structures in computed tomography (CT) and fluoroscopic interventions. Apart from pharmacological toxicity, iRCM can cause drug hypersensitivity reactions (DHR), either immediate (IHR; occurring $\leq$ 1 h after administration) or nonimmediate (NIHR; occurring from 1 h to several days after iRCM administration).[1] Both types of DHR can be classified as allergic or non-allergic DHR depending on the skin test (ST) result.[2–4] Although these contrast agents are generally considered to be safe, especially the nonionic low or iso-osmolar products currently used, IHRs and NIHRs are reported in about 1%–3% of iRCM injections.[1,2,5] The main strategy for minimizing iRCM allergic DHR at our center[6] has been avoiding the culprit iRCM (positive skin tested iRCM), banning cross-reactive iRCMs, and identifying non cross-reactive agents by means of drug allergy work-up.[1,3,7,8] This strategy is in accordance with the recently published European recommendations[11] on allergy work-up for iRCM, which now also include algorithms to cover emergency situations when a drug allergy work-up is not feasible. Alternatively, avoidance of the culprit iRCM and/or use of premedication in certains situations can be used; however, there is limited evidence that this strategy can prevent recurrent reactions.[10,11]

Skin testing is a useful tool for diagnosis of iRCM allergic DHRs, and ST may play an important role in selecting a safe alternative iRCM in allergic patients with a specificity of 96–100%.[1,2,12,13] When ST is performed 2 to 6 months after the reaction, up to 50% of patients with IHRs, and 47% of those with NIHRs show positive ST.[1,2] In real-life clinical settings, the negative predictive value (NPV) of iRCM ST is above 90%.[6]

Precision medicine is a novel approach to patient management that is based on different endotypes.[14] In asthma, significant progress has been made in defining clinical phenotypes that are linked to underlying endotypes.[15,16] However, the definition of phenotypes and endotypes specific to DHRs is hampered by a lack of biological markers, except for tryptase, and a few serum-specific IgEs.[14]

At present, clinical phenotyping of DHRs to iRCM follows an *a priori* determined classification based on patient characteristics, clinical history, and drug allergy work-up results. In this study, we hypothesized that amongst a heterogeneous population of patients with suspicion of iRCM DHRs, clinically relevant groupings can be developed and described that will supersede the pre-existing *a priori* classifications.

Cluster analysis is defined as a broad set of unsupervised machine learning techniques that can be used to identify distinct subgroups or clusters within a set of data. This study aimed to distinguish different characteristics among patients with a suspicion of a DHR to iRCM based on cluster analysis of data from a large drug allergy and hypersensitivity database.

METHODS

Patients and data extraction

A retrospective study was performed using data extracted from the *Drug Allergy and Hypersensitivity Database (DAHD)* of the Allergy Unit, University Hospital of Montpellier, Montpellier, France. All referred patients with suspicion of iRCM DHR during February 2001 to December 2019 with either confirmed positive ST or confirmed negative ST were included in the analysis. Of this population, 597 (2001–2014) have been previously analyzed (Schrijvers et al).[6]

The protocol for this study was approved by the Institutional Review Board of the University Hospital of Montpellier (IRB-MTP 2020-00692). Written informed consent was obtained from study participants at the time of allergy work-up.

Retrieved data included demographic data, symptoms, and chronology of the DHR, culprit iRCM used during the procedure, delay between the reaction, and the date of tests, chronology, and identified iRCMs from positive ST results. Our study protocol did not include drug provocation tests (DPT) to iRCM except in rare selected NIHR cases. If more than 1 DHR occurred, the most severe reaction was included in the analysis.

Index reactions were classified as IHR or NIHR based on the clinical history. ST was typically performed using a set of 10 iRCMs that are available in France (ie, amidotrizoate (Radioselectan®), ioxitalamate (Telebrix®), iopamidol (Iopamiron®), iohexol (Omnipaque®), ioversol (Optiray/Optiject®), iopromide (Ultravist®), iomeprol (Iomeron®), iobitridol (Xenetix®), iodixanol (Visipaque®), and ioxaglate (Hexabrix®)), as previously described.[6,17] Briefly, skin prick tests were performed, and if negative after 15-minute reading, they were followed by intradermal tests (IDT). Reading at 20 minutes was performed for IHRs, and delayed reading of IDT was performed for up to 7 days for NIHRs. For patients with unknown chronology, an immediate reading was always performed. The decision to indicate a delayed reading was taken by the allergist, according to the semiology of the reaction (if known). All patients were discharged with the contact data of the allergy team, in case of subsequent requests. The chronology of the positive ST was assigned separately from that of the index reaction, but following the same classification (ie, immediate and nonimmediate ST reactors), and was compared to that of the index reaction.

For the analysis, iRCMs were assigned to1 of the 4 following subgroups according to their chemical structures: group SC (iodixanol, iohexol, iomeprol, iopamidol, iopromide, and ioversol), which contained at least 1 identical N-(2,3-dihydroxypropyl) carbamoyl ***s***ide ***c***hain [ie, "similar side chain"; of note, iopamidol contains 2 N-(2,3-dihydroxy***iso***propyl) carbamoyl side chains]; group TE (ioxitalamate and ioxaglate) with ionic monomer and dimer; group X (iobitridol); and, group R (amidotrizoate). In the SC group, the number of identical N-(2,3-dihydroxyisopropyl) carbamoyl side chains differ: iodixanol (4), iohexol (2), iomeprol (2), and iopromide (1). Cross-reactivity was defined as ST positivity to 2 or more iRCMs.

Statistical analysis and cluster build-up

All analyses were performed using SPSS Statistics version 18.0 (SPSS, Inc., Chicago, IL, USA). Categorical data are presented as number and percentage (%). Continuous data are expressed as median and interquartile range or range (minimum, maximum) for non-normally distributed data. Chi-square test was used to compare categorical data between groups, whereas Mann-Whitney *U* test was used to compare continuous non-normally distributed data. Binary logistic regression was used to identify risk factors for having a positive ST to iRCM. Parameters with a *p*-value less than 0.25 in univariate logistic regression were included multivariate analysis. A *p*-value less than 0.05 indicates statistical significance.

The TwoStep cluster method was used to determine cluster numbers. TwoStep cluster analysis[18] is a hybrid approach that first uses a distance measure to separate groups, and then a probabilistic approach (similar to latent class analysis) to identify the optimal subgroup model. This technique has several advantages compared to more traditional techniques, such as determining the number of clusters based on a statistical measure of fit (eg, Schwarz's Bayesian Information Criterion [BIC]) rather than on an arbitrary choice, using categorical and continuous variables simultaneously, and being able to handle large datasets. Automatic selection was favored because it prevented any intervention in the analysis. Smaller BIC values indicate better models. Model quality was evaluated as poor, fair, or good. A cluster ratio (the number of participants in the largest over the smallest obtained cluster) inferior to 3 was considered acceptable (ie, no cluster is more than 3 times the size of another cluster). For each cluster, the variables' importance chart (ranging from 0 to 1 for each variable) was analyzed.

All patients referred with suspicion of DHR to iRCM were included for cluster construction. The following variables, which were reported to be risk factors for iRCM allergy in previous studies,[1,6,19] were used for cluster build-up (i) clinical

manifestations (anaphylactic shock, anaphylaxis, urticaria/angioedema, maculopapular exanthema [MPE], isolated malaise, isolated bronchospasm, MPE with signs of severity (systemic involvement, including fever, eosinophilia, hepatitis, and cytopenia),[20] fixed drug eruption, other manifestations (intense isolated signs requiring medical intervention like cardiac signs [tachycardia, arrythmia], digestive signs [abdominal pain, vomiting], arthralgias and unknown); (ii) chronology of the index reaction (IHRs, NIHRs, and unknown); (iii) delay between index reaction and ST (years); (iv) culprit iRCMs (all 10 iRCMs as described above); and, (v) number of episodes of DHR to iRCMs (single, multiple, and unknown). The result of the test, the number of confirmed positive STs to iRCMs, and the chronology of reactivity (see above) were used as evaluation fields (ie, as description of the resulting clusters) (Supplementary Figure 1).

In our previous study,[6] 7 of 56 patients with unknown chronology of their index reaction (12.5%) were found to be allergic. After reviewing their files in detail, we observed that delayed positive reading ST was observed in 2 patients with non-severe MPE, and in 3 patients with MPE with severity signs. In 1 patient with anaphylaxis, STs were positive on immediate reading, and for another patient with MPE, the chronology of the ST reading was unknown. Therefore, for the present study (including 56 patients with unknown chronology from 841 new patients [6.6%] since our previous study), we classified the "unknown" index reactions as IHRs or NIHRs according to the semiology of the reaction. For urticaria/angioedema, the IHR classification was favored even though delayed urticaria/angioedema is possible. However, awareness about NIHR is low (even among fellow physicians), and when a patient is labeled as "allergic to iodine" following an iRCM administration, it is most likely that this reaction was pointed out by the medical staff soon after the administration of the iRCM. Patients still assigned in this database as "unknown" are those with both unknown semiology and unknown chronology.

According to the European recommendations on iRCM DHR,[11] *"either re-exposition or DPT can be performed to confirm tolerance to a skin test-negative iRCM"*. We also included data on reexposure of patients to a negatively tested iRCM, which was available from our previous study for 233 patients. This information was included in the evaluation fields, but not in the cluster build-up. However, no such data was available for the remaining 841 new patients.

Cluster analysis of the sub-group of 153 patients with confirmed ST positivity was also performed. Similar variables were used to build up the clusters, as follows: (i) clinical manifestations (anaphylactic shock, anaphylaxis, urticaria/angioedema, maculopapular exanthema, other manifestations, and unknown); (ii) chronology of the index reaction (IHRs and NIHRs); (iii) delay between index reaction and ST (years); and, (iv) culprit iRCM groups (SC, TE, X, and R). The chronology of ST positivity, the number and type of confirmed positive iRCMs, and the number of DHR episodes (single or multiple suspicion) were used as evaluation fields (Supplementary Figure 2).

RESULTS

All-patient characteristics

A total of 1439 patients with suspicion of having a DHR to iRCM who underwent a drug allergy work-up were included in this study. The male:female ratio was 1:3. Asthma and atopy were reported in 9%, and 31.1% of patients, respectively. The median time delay between the index reaction and ST was 3.5 years (interquartile range [IQR]: 1 day - 72.6 years). The chronology of the index reaction was immediate in 77.1%, and nonimmediate in 22.4%. Urticaria and/or angioedema (28.7%) were the most common clinical manifestations, followed by anaphylaxis (20.9%), MPE (20.5%), and anaphylactic shock (17.9%). Multiple episodes were reported in 11.1% of patients (Table 1). Positive STs were shown in 153 patients (10.6%).

Characteristics of iRCM allergic patients

Allergic and non-allergic patients differed with respect to gender, delay between index reaction and ST, clinical history, and chronology of the index reaction (Table 1). When analyzed separately, male gender, anaphylactic shock, and having an IHR increased the risk of having positive ST

Clinical characteristics	Total (N = 1439)	Positive STs (n = 153) N (%)	Negative STs (n = 1286) N (%)	*p*-value
Gender				***0.02***
Male	477 (33.2)	64 (41.8)	413 (32.1)	
Female	962 (66.8)	89 (58.2)	873 (67.9)	
Asthma	130 (9.0)	9 (5.9)	121 (9.4)	0.15
Atopy	447/1437 (31.1)	45/153 (29.4)	402/1284 (31.3)	0.79
Median time delay reaction/tests (IQR), (range)	3.5 y (4.7 Mo-17.8 y) (1 d-72.6 y)	5 Mo (2.4 Mo-5.3 y) (1 d-51.9 y)	4.8 y (5.6 Mo-19.1 y) (1 d-72.6 y)	< ***0.001***
Clinical manifestations				< ***0.001***
Anaphylactic shock	257 (17.9)	53 (34.6)	204 (15.9)	
Anaphylaxis	302 (20.9)	23 (15.0)	279 (21.7)	
Urticaria/angioedema	413 (28.7)	22 (14.4)	391 (30.4)	
Isolated bronchospasm	46 (3.2)	1 (0.7)	45 (3.5)	
Isolated malaise	30 (2.1)	1 (0.7)	29 (2.3)	
MPE	295 (20.5)	45 (29.4)	250 (19.4)	
MPE with severity signs[a]	18 (1.2)	5 (3.2)	13 (1.0)	
Fixed drug eruption	4 (0.3)	1 (0.7)	3 (0.2)	
Others[b]	30 (2.1)	1[c] (0.7)	29 (2.3)	
Unknown	44 (3.1)	1 (0.7)	43 (3.3)	
Chronology of the index reaction				< ***0.001***
IHR	1110 (77.1)	98 (64.1)	1012 (78.7)	
NIHR	322 (22.4)	55 (35.9)	267 (20.8)	
Unknown	7 (0.5)	0	7 (0.5)	
Multiple episodes				0.12
Yes	160 (11.1)	17 (11.1)	143 (11.1)	
No	1244 (86.5)	136 (88.9)	1108 (86.2)	
Unknown	35 (2.4)	0	35 (2.7)	
Culprit iRCMs				< ***0.001***
Amidotrizoate	1 (0.1)	0	1 (0.1)	
Iobitridol	119 (8.3)	15 (9.8)	104 (8.1)	
Iodixanol	52 (3.6)	17 (11.1)	35 (2.7)	
Iohexol	51 (3.5)	12 (7.8)	39 (3)	
Iomeprol	150 (10.4)	25 (16.3)	125 (9.7)	
Iopamidol	20 (1.4)	1 (0.7)	19 (1.5)	
Iopromide	67 (4.7)	15 (9.8)	52 (4)	
Ioversol	45 (3.1)	6 (3.9)	39 (3)	
Ioxagate	23 (1.6)	6 (3.9)	17 (1.3)	
Ioxitamate	9 (0.6)	1 (0.7)	8 (0.6)	
Unknown	902 (62.7)	55 (36)	847 (65.9)	

Table 1. Demographic and clinical characteristics of all study patients, and compared between those with positive and negative skin tests.
Abbreviations: d, day; iRCM, iodinated radiocontrast media; Mo, months; MPE, maculopapular exanthema; IHR, immediate hypersensitivity reaction; NIHR, non-immediate hypersensitivity reaction; ST, skin tests; y, years. [a]*MPE with severity signs: systemic involvement (eg, fever, eosinophilia, hepatitis, cytopenia).* [b]*Intense isolated signs requiring medical intervention like cardiac signs (tachycardia, arrythmia), digestive signs (abdominal pain, vomiting), arthralgias.* [c]*This patient had vomiting and abdominal pain*

Risk factors	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*	Adjusted OR	95% CI	*p*
Sex						
Female	1					
Male	**1.52**	**1.08-2.14**	***0.02***	1.39	0.97–1.98	0.07
Asthma						
No	1					
Yes	0.60	0.30–1.21	0.15	0.68	0.33–1.42	0.31
Atopy						
No	1					
Yes	0.91	0.63–1.32	0.63			
Delay reaction/tests	**0.995**	**0.993-0.997**	***<0.001***	**0.995**	**0.993-0.997**	***<0.001***
Clinical manifestation						
Other reactions[a]	1					
Anaphylactic shock	**2.81**	**1.95-4.05**	***<0.001***	**4.68**	**3.01-7.27**	***<0.001***
Anaphylaxis	0.64	0.40–1.01	0.06	1.16	0.70–1.94	0.56
Chronology of the index reaction						
NIHR	1					
IHR	**2.13**	**1.49-3.04**	***<0.001***	**2.51**	**1.67-3.78**	***<0.001***
Multiple episodes						
No	1					
Yes	0.97	0.57–1.65	0.91			

Table 2. Logistic regression analysis to identify risk factors for iRCM allergy (positive ST). *Abbreviations: iRCM, iodinated radiocontrast media; OR, odds ratio; ST, skin tests.* [a]***Other reactions i.e.,*** *urticaria/angioedema, isolated bronchospasm, isolated malaise, maculopapular exanthema, others (from the previous Table 1), and unknown*

Clinical characteristics	Positive ST result (N = 150)[a]		p-value
	IHRs confirmed (n = 97) N (%)	NIHRs confirmed (n = 53) N (%)	
Male	40 (41.2)	22 (41.5)	0.97
Asthma	5 (5.2)	2 (3.8)	0.70
Atopy	31 (32)	13 (24.5)	0.34
Median age of reaction (y;range)	55 (13–55)	58 (13–90)	0.13
Median time delay reaction/tests (IQR), (range)	7 Mo (2 Mo-6.3 y) (1 d-51.9 y)	5 Mo (3.2 Mo-2.8 y) (24 d-24.8 y)	0.69
Clinical manifestations			< ***0.001***
Anaphylactic shock	49 (50.5)	1 (1.9)	
Anaphylaxis	22 (22.7)	1 (1.9)	
Urticaria/angioedema	15 (15.5)	7 (13.2)	
MPE	8 (8.2)	37 (69.8)	
MPE with severity signs[b]	0	5 (9.4)	
Others[c]	3 (3.1)	1 (1.9)	
Unknown	0	1 (1.9)	
Chronology of the index reaction			< ***0.001***
IHR	93 (95.9)	2 (3.8)	
NIHR	4 (4.1)	51 (96.2)	
Concordance between chronology of index reaction and that of tests	93 (95.9)	51 (96.2)	0.92
Multiple episodes	10 (10.3)	7 (13.2)	0.59
Positive ST drug class			< ***0.001***
Single positive (ie, for 1 class of iRCM)	66 (68)	14 (26.4)	
TE	34 (51.5)	9 (64.3)	
SC	21 (31.8)	3 (21.4)	
X	8 (12.1)	2 (14.3)	
R	3 (4.6)	–	
Multiple positive (ie, iRCM from at least 2 classes)	31 (32)	39 (73.6)	
SC	12 (38.7)	13 (33.3)	
SC/TE	8 (25.8)	10 (25.6)	
SC/X	5 (16.1)	9 (23.1)	
Other profiles	6 (19.4)	7 (18.0)	

Table 3. Demographic data, clinical characteristics, and test results compared between the immediate and non-immediate allergic groups (according to the chronology of the positive ST). *Abbreviations: d, day(s); IHR, immediate hypersensitivity reaction; iRCM, iodinated radiocontrast media; Mo, months; MPE, maculopapular exanthema; NIHR, non-immediate hypersensitivity reaction; R, amidotrizoate; SC (side chain), iodixanol/iohexol/iomeprol/iopamidol/iopromide/ioversol; ST, skin test; TE, ioxitalamate/ioxaglate; X, iobitridol; y, years.* [a]*3 patients excluded because of undetermined chronology of ST.* [b]*MPE with severity signs:* systemic involvement (eg, fever, eosinophilia, hepatitis, cytopenia). [c]*Others: IHR: abdominal pain and vomit (n = 1), isolated bronchospasm (n = 1), isolated malaise (n = 1), and NIHR: fixed drug eruption (n = 1)*

results. However, in multivariate analysis, only a history of anaphylactic shock and chronology of IHR were shown to be significant independent risk factors for allergy with adjusted odds ratios (aOR) of 4.68 (95%CI: 3.01–7.27, $p < 0.001$) and 2.51 (95%CI: 1.67–3.78, $p < 0.001$), respectively. Longer delay time between index reaction and ST was found to be predictive of negative ST (aOR: 0.995, 95%CI: 0.993–0.997; $p < 0.001$) (Table 2).

Clusters	Cluster 1 N (%)	Cluster 2 N (%)	Cluster 3 N (%)	Cluster 4 N (%)	Cluster 5 N (%)
Cluster size	325 (22.6)	327 (22.7)	150 (10.4)	354 (24.6)	283 (19.7)
Variables and their importance as predictors (from 0 to 1)					
Chronology of the index reaction (1)					
IHR	-	**326 (99.4)**	**149 (99.3)**	**354 (100)**	**281 (99.3)**
NIHR	**322 (99.1)**	-	-	-	-
Unknown	3 (0.9)	1 (0.6)	1 (0.7)	-	2 (0.7)
Multiple episodes (0.79)					
Yes	*44 (13.5)*	-	**116 (77.3)**	-	-
No	**280 (86.2)**	**327 (100)**	-	**354 (100)**	**283 (100)**
Unknown	1 (0.3)	-	*34 (22.7)*	-	-
Clinical manifestations (0.64)					
Anaphylactic shock	15 (4.6)	80 (24.5)	*35 (23.3)*	-	*127 (44.9)*
Anaphylaxis	38 (11.7)	*83 (25.4)*	26 (17.3)	-	**155 (54.7)**
Urticaria/angioedema	*80 (24.6)*	**113 (34.6)**	**45 (30)**	**175 (49.4)**	-
Isolated malaise	1 (0.3)	3 (0.9)	3 (2)	23 (6.5)	-
Isolated bronchospasm	6 (1.8)	7 (2.1)	7 (4.7)	26 (7.3)	-
MPE	**160 (49.2)**	35 (10.7)	22 (14.7)	*78 (22)*	-
MPE with severity signs[a]	15 (4.6)	-	3 (2)	-	-
Fixed drug eruption	3 (0.9)	-	-	-	1 (0.4)
Other	4 (1.2)	3 (0.9)	3 (2)	20 (5.7)	-
Unknown	3 (0.9)	3 (0.9)	6 (4)	32 (9)	-
Culprit iRCMs (0.63)					
SC	*126 (38.8)*	**228 (69.8)**	*30 (20)*	-	1 (0.3)
Iodixanol	34 (10.4)	17 (5.2)	1 (0.7)	-	-
Iohexol	20 (6.2)	25 (7.7)	5 (3.3)	-	1 (0.3)
Iomeprol	32 (9.9)	102 (31.2)	16 (10.7)	-	-
Iopamidol	3 (0.9)	15 (4.6)	2 (1.3)	-	-
Iopromide	17 (5.2)	46 (14.1)	4 (2.7)	-	-
Ioversol	20 (6.2)	23 (7)	2 (1.3)	-	-
TE	6 (1.8)	23 (7)	3 (2)	-	-
X	25 (7.7)	*76 (23.2)*	18 (12)	-	-
R	-	-	-	1 (0.3)	-

Unknown	**168 (51.7)**	-	**99 (66)**	**353 (99.7)**	**282 (99.7)**
Delay reaction/tests (0.26) (IQR), (range)	9.9 Mo (3.4 Mo-5.9 y) (4 d-64.6 y)	4.5 Mo (2.1 Mo-1.4 y) (1 d-30.4 y)	5.8 y (7.4 Mo-16.1 y) (1 d-20.8 y)	14.7 y (5.0 y-26.9 y) (10 d-72.6 y)	15.4 y (4.2 y-28.8 y) (9 d-51.9 y)
Evaluation fields					
Male patients	113 (34.8)	116 (35.7)	54 (36.0)	109 (30.8)	85 (30.0)
Allergic	55 (16.9)	55 (16.5)	8 (5.3)	12 (3.4)	24 (8.5)
Reexposed to iRCM[b]	44 (18.8)	29 (12.4)	41 (17.6)	72 (30.9)	47 (20.1)
Tolerance to re-exposure[b]	38 (86.3)	28 (96.5)	37 (90.2)	69 (95.3)	45 (95.7)

Table 4. Cluster analysis (automatic solution) among all patients (N = 1439). *The most prevalence characteristic for each variable is in bold. The second most prevalence characteristic for each variable is in italic. Abbreviations: d, day(s); Mo, months; MPE, maculopapular exanthema; IHR, immediate hypersensitivity reaction; NIHR, non-immediate hypersensitivity reaction; R, amidotrizoate; SC, iodixanol/iohexol/iomeprol/iopamidol/iopromide/ioversol; TE, ioxitalamate/ioxaglate; X, iobitridol; y, years.* [a]***MPE with severity signs:*** *systemic involvement (eg, fever, eosinophilia, hepatitis, cytopenia).* [b]*Of 233 patients for whom the data was available*

Clinical characteristics and test results for the allergic group broken down by chronology of reactivity in ST are shown in Table 3. Immediate reactors accounted for two-thirds of allergic patients. Concordance between the chronology of the index reaction and that of tests was 96% for all DHRs (95.9% for IHRs, and 96.2% for NIHRs).

In 30 cases (2%), the allergy work-up was performed for atypical reactions, eg, intense isolated signs requiring medical intervention like cardiac signs (tachycardia, arrythmia), digestive signs (abdominal pain, vomiting), arthralgias. One patient with severe digestive symptoms displayed positive ST.

Cross-reactivity was noticed in three-quarters of non-immediate reactors, but not more than one-third of immediate reactors.

All-patient cluster analysis

The solution proposed by the automatic cluster analysis categorized the 1439 patients into 5 clusters with a fair quality of clustering and an optimal ratio (2.3) of the cluster sizes (Table 4 and Fig. 1A).

Cluster 1 contained all and almost only patients that had had an NIHR. Concerning the clinical manifestations, 80% were cutaneous with MPE accounting for more than half of these cases, followed by urticaria/angioedema. Cluster 1 contained 83% of MPE with severity signs. Of note, 1 in 5 patients described symptoms compatible with an immediate reaction (anaphylaxis with or without shock, isolated bronchospasm, or malaise). The culprit was known in half of cases, and the culprit was most often a group SC iRCM. Half of patients were tested within 9.9 months (IQR: 3.4 months – 5.9 years) after the reaction. Multiple episodes were rare in this group (13.5%).

Cluster 2 comprised virtually only patients with IHRs, all with known culprit iRCM (mostly group SC followed by X) and a single episode of DHR, tested less than 6 months after the reaction (IQR: 2.1 months - 1.4 years). In this cluster, half of patients had had anaphylaxis (with or without shock) and one-third had urticaria/angioedema.

Cluster 3 was similar to cluster 2 since it also comprised IHRs, especially anaphylaxis (40.6%) and urticaria (30%). However and in contrast to

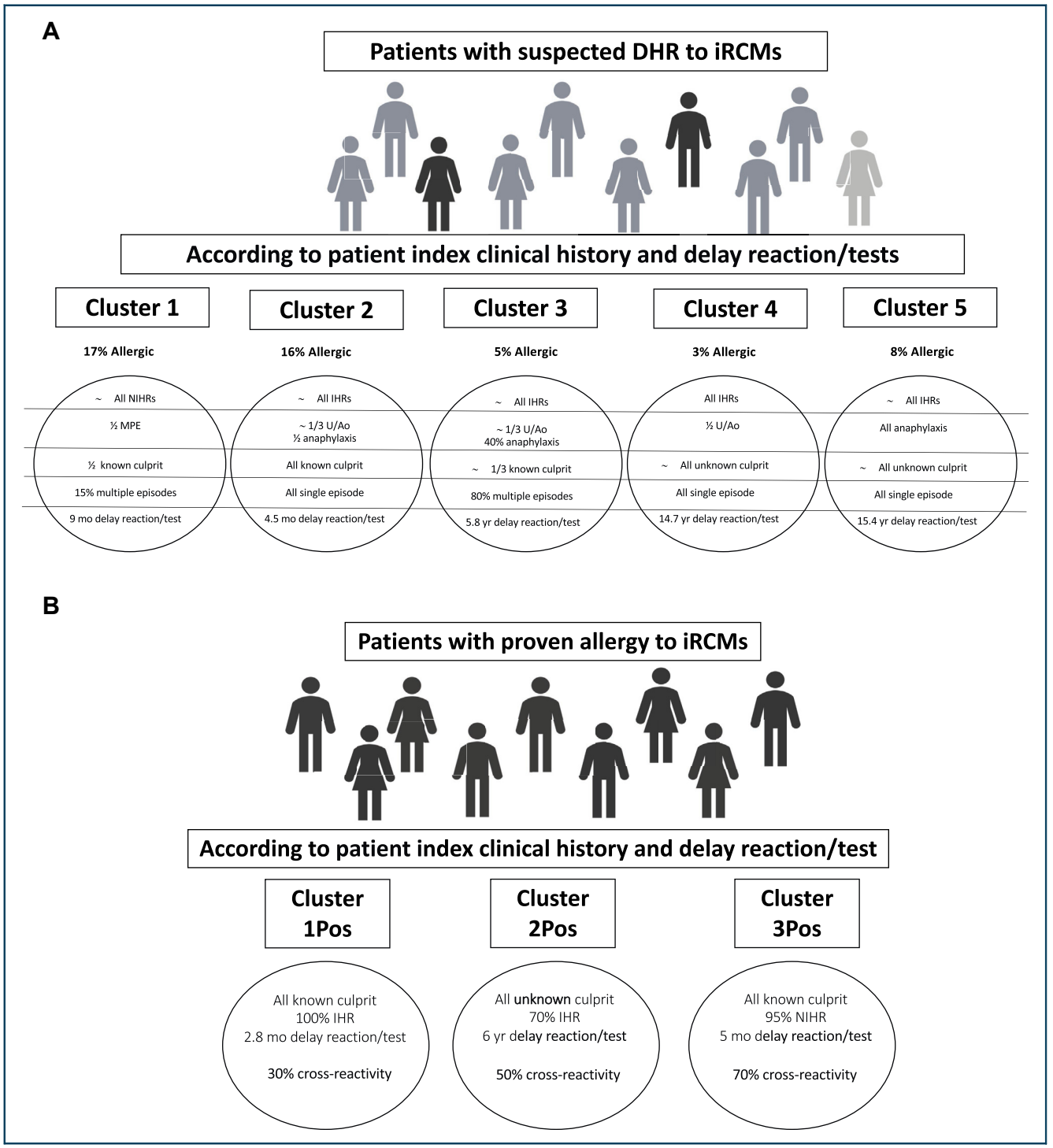

Fig. 1 Summary of the clinical phenotypes of patients identified by cluster analysis. Whenever possible, values are rounded-up to facilitate easier reading of the clusters. (A). Automatic cluster analysis of patients with suspected DHR to iRCM (N = 1439) (B). Automatic cluster analysis of patients with proven allergy to iRCM (ST positive) patients (n = 153). Legend: IHR, *immediate hypersensitivity reaction;* MPE, *maculo-papular exanthema;* NIHR, *non-immediate hypersensitivity reaction;* U/AO, *urticaria/angioedema*

cluster 2, culprit iRCMs were unknown in two-thirds. Half of patients were tested within 6 years (IQR: 7.4 months - 16.1 years) after their reaction, and three-quarters had experienced multiple episodes of reaction.

Clusters 4 and 5 were virtually identical, except for the type of clinical manifestation. Both groups comprised IHRs with a single episode of DHR that was induced by unknown culprits, and that was tested 14–15 years after the index reaction.

Clusters	Cluster 1Pos N (%)	Cluster 2Pos N (%)	Cluster 3Pos N (%)
Cluster size	58 (37.9)	55 (35.9)	40 (26.1)
Variables and their importance as predictors (from 0 to 1)			
Culprit iRCMs (1)			
SC	**42 (72.4)**	**-**	**33 (82.5)**
Iodixanol	6 (10.3)	-	11 (27.5)
Iohexol	4 (6.9)	-	8 (20)
Iomeprol	18 (31)	-	7 (17.5)
Iopromide	12 (20.7)	-	3 (7.5)
Ioversol	2 (3.4)	-	4 (10)
TE	6 (10.3)	-	1 (2.5)
Ioxaglate	6 (10.3)	-	-
Ioxitalamate	-	-	1 (2.5)
X	*9 (15.5)*	-	*6 (15)*
SC/X	1 (1.7)	-	-
Unknown	-	***55 (100)***	-
Chronology of the index reaction (0.69)			
IHR	**58 (100)**	**38 (69.1)**	2 (5)
NIHR	-	17 (30.9)	**38 (95)**
Clinical manifestations (0.51)			
Anaphylactic shock	**37 (63.8)**	**16 (29.1)**	-
Anaphylaxis	*13 (22.4)*	10 (18.2)	-
Urticaria/angioedema	8 (13.8)	11 (20.0)	3 (7.5)
Isolated malaise	-	1 (1.8)	-
Isolated bronchospasm	-	1 (1.8)	-
Abdominal pain/vomiting	-	1 (1.8)	-
MPE	-	*15 (27.2)*	**30 (75)**
MPE with severity signs	-	-	*5 (12.5)*
Fixed drug eruption	-	-	1 (2.5)
Unknown	-	-	1 (2.5)
Median delay reaction/tests (0.31) (IQR), (range)	2.8 Mo (1.6 Mo-1.3 y) (1 d-10.3 y)	6.0 y (4.4 Mo-19.6 y) (1 Mo-51.9 y)	5.0 Mo (3.1 Mo-1.1 y) (25 d-14.3 y)
Evaluation fields			
Male patients	25 (43.1)	22 (40)	17 (42.5)
Multiple episodes	5 (8.6)	5 (9.1)	7 (17.5)
Test result			
Single positive	39 (67.2)	30 (54.5)	13 (32.5)
Amidotrizoate	-	3 (5.4)	-
Iobitridol	8 (13.8)	-	2 (5)
Iodixanol	5 (8.6)	2 (3.6)	7 (17.5)
Iohexol	-	1 (1.8)	1 (2.5)

(continued)

Clusters	Cluster 1Pos N (%)	Cluster 2Pos N (%)	Cluster 3Pos N (%)
Iomeprol	13 (22.4)	5 (9)	1 (2.5)
Iopamidol	1 (1.7)	1 (1.8)	–
Iopromide	6 (10.3)	7 (12.7)	–
Ioversol	–	–	1 (2.5)
Ioxaglate	6 (10.3)	6 (10.9)	–
Ioxitalamate	–	5 (9)	1 (2.5)
Multiple positive	19 (32.8)	25 (45.5)	27 (67.5)
within SC	10/19 (52.6)	4/25 (16)	11/27 (40.7)
SC/TE	5/19 (26.3)	7/25 (28)	6/27 (22.2)
SC/X	2/19 (10.5)	3/25 (12)	9/27 (33.3)
Others	2/19 (10.5)	11/25 (44)	1/27 (3.7)
Chronology of ST positivity			
IHR	55 (94.8)	39 (70.9)	3 (7.5)
NIHR	1 (1.7)	15 (27.3)	37 (92.5)
Undetermined	2 (3.5)	1 (1.8)	–
Reexposed to iRCM[a]	6 (37.5)	7 (43.7)	3 (18.7)
Tolerance to re-exposure[a]	5 (83.3)	7 (100)	3 (100)

Table 5. (Continued) Cluster analysis (automatic solution) among 153 patients with positive ST to iRCM. *The most prevalence characteristic for each variable is in bold. The second most prevalence characteristic for each variable is in italic.* ***Abbreviations****: d, day(s); Mo, months; MPE, maculopapular exanthema; IHR, immediate hypersensitivity reaction; iRCM, iodinated radiocontrast media; NIHR, non-immediate hypersensitivity reaction; R, amidotrizoate; SC, iodixanol/iohexol/iomeprol/iopamidol/iopromide/ioversol; ST, skin test; TE, ioxitalamate/ioxaglate; X, iobitridol; y, years. [a]16 patients of 233 re-exposed patients belong to clusters 1,2,3Pos. The percentages for re-exposure and tolerance are therefore calculated as per 16*

Regarding the clinical manifestations, cluster 5 contained virtually only anaphylactic events, whereas cluster 4 included various reactions, but no anaphylaxis.

In terms of size, cluster 4 was the largest (24.6%), followed by clusters 1 and 2 (22.6% and 22.7%, respectively). Confirmed allergies were more frequent in clusters 1 (16.9%) and 2 (16.5%). When data on reexposure was taken into account, clusters 1, 3, and 4 accounted for about 20% of reexposures each, whereas the well-identified "immediate" cluster 2 accounted for 12.4% of reexposures. The highest percentage of reexposure per cluster belonged to cluster 4. Tolerance to reexposure was high in the "immediate" clusters (>90% in clusters 2–5), and it was lower, but still acceptable in cluster 1 (86%).

Cluster analysis of iRCM allergic patients

Among the 153 patients with ST-confirmed allergy to iRCMs, 3 clusters were identified from the automatically determined TwoStep cluster analysis (Table 5 and Fig. 1B). The quality of the clusters was shown to be fair with optimal ratio (1.45) of the cluster sizes. All patients in cluster 1Pos had a clinical history of IHR, known culprit iRCMs (SC-72.4%, X-15.5%, TE-10.3%, and SC/X-1.7%), and a median delay between index reaction and ST of 2.8 months (IQR: 1.6 months – 1.3 years). Most of them had presented with anaphylactic shock (63.8%), followed by anaphylaxis (22.4%) and urticaria/angioedema (13.8%). Cluster 3Pos was also homogenous, comprising 95% NIHRs, all with known culprit iRCMs (SC-82.5%, X-15%, and TE-2.5%), and a median of 5 months delay between index reaction and ST (IQR: 3.1 Mo-1.1 years). MPE with or without severity signs (87.5%) was the main clinical manifestation within this group. Multiple episodes (17.5%) and multiple positive tests (67.5%) to iRCMs were more prevalent in cluster 3Pos. Patients in cluster 2Pos were a more heterogenous population containing both IHRs (69.1%) and NIHRs (30.9%), all of them with an undetermined culprit iRCM, and a median delay between index reaction and ST of 6 years (IQR: 4.4 months – 19.6 years).

The transition between the clusters before and after the allergy work-up is represented in Supplementary Figure 3: most patients from the

well-defined clusters 1Pos (53 of 58 patients, 91.4%) and 3Pos (38 of 40 patients, 95%) came from the well-defined Cluster 2 and 1, respectively.

DISCUSSION

Clinicians are frequently confronted with patients with a prior iRCM DHR. When requiring a repeat iRCM administration, several approaches have been suggested. Recent guidelines recommend a clinical history-based drug allergy workup in severe cases.[11] Given the lack of reliable biomarkers, the clinical data is paramount to guide these evaluations. Here, we used cluster analysis on a large iRCM DHR patient database to confirm, challenge, or add hitherto unknown prototypic patterns via machine learning. We observed 5 distinct clusters, each representing a prototypic patient population with an associated risk for allergy.

The purpose of cluster analysis is to identify subgroups in which observations assigned to the same group are similar with respect to 1 or more variables, while observations assigned to different groups are dissimilar. This kind of unsupervised approach may confirm, challenge, or add to existing knowledge by revealing hitherto unknown patterns of clinical manifestations or reactivity during the drug allergy work-up.

By including more than 1400 patients with a binary diagnosis (allergic/non-allergic) in our analysis, we were able to assure a powerful set of data that includes a variety of iRCM DHR clinical presentations. Phenotyping these patients using cluster analysis yielded 5 prototypic clinical profiles. Using classical statistical methods, such as logistic regression in this work and in line with the prevailing literature, both the chronology and semiology of the index reaction were found to be strong predictors of allergy. Chronology of the index reaction was the most important discriminator due to its ability to strongly differentiate between IHRs and NIHRs amongst the clusters, with patients in cluster 1 being NIHRs, and those in clusters 2 to 4 being IHRs. When analyzed in detail, these clusters provide the following valuable information: (i) groupings with relatively well-defined culprit iRCMs and highly compatible semiology (clusters 1 and 2) are tested quite rapidly after their reaction and comprise rarely (cluster 1) or not at all (cluster 2) multiple events; (ii) these are the groupings with the highest prevalence of allergy, but even so, only around 1 in 6 patients is allergic; (iii) in patients with IHRs tested remotely after their reaction (more than 1 or 2 decades), the prevalence of allergy is below 10%, and up to 3.4% in the absence of anaphylaxis; and, (iv) cross-reactivity involves almost three-quarters of non-immediate reactors, but not more than one-third of immediate reactors.[6,19]

The value of the cluster approach in this clinical setting is that it identifies patterns beyond individual independent risk factors for allergy to iRCM. For instance, between clusters 2 and 5, both with mainly anaphylactic IHR, certain variables differ (whether or not the culprit is known, delay reaction/tests), and the prevalence of allergy is divided by 2 despite similar strong predictors, such as chronology and semiology. Other data appears less open to interpretation, like cluster 3, which seems to be a "catch-all" category.

Similar to a previous study by our research group,[6] approximately one-tenth of our study population was found to have positive ST to iRCMs, with two-thirds of patients being immediate and the other one-third nonimmediate reactors. This positivity rate is lower than several previous studies that reported a prevalence of confirmed DHR ranging from 19.6% to 50% if the patients were tested within 2 to 6 months after the reaction.[1,19,21,22] These differences between and among studies may be explained by differences in study design (prospective *vs* restrospective), drug allergy work-up method (ST with/without DPT), and delaybetween index reaction and ST. Taking into account the high NPV of iRCM STs in real-life settings (Schrijvers et al.[6] 93.1%; Caimmi et al[17] 96.6%) and the risk-benefit balance of iRCM administration outside of a radiographic exam, the drug allergy work-up for iRCM in our unit is essentially based on ST.[6,17] This approach is in accordance with the current European and international expert consensus, which suggests that iRCM provocation be performed only in selected cases that have a risk of severe reactions.[7]

Although asthma, atopic status, and gender were reported in some studies to be risk factors for confirmed DHR to iRCMs,[5,23–25] we were not able confirm these associations in our large data set

and using multivariate analysis. We found history of anaphylactic shock to be the strongest risk factor associated with confirmed allergy to iRCMs. In addition, IHRs and shorter delay for reaction/test were also shown to be significant independent risk factors that predict a positive ST outcome. Interestingly, we did not find anaphylaxis without shock to be an independent risk factor. Similarly, Kim, et al[26] found a higher rate of positive ST to iRCMs in anaphylactic shock compared to anaphylaxis without shock. Clement et al[21] reported that the frequency of allergy to iRCMs increased with clinical severity, and also that cardiovascular signs were strongly associated with allergy. If anaphylaxis (not only anaphylactic shock) is regularly associated with a positive outcome of the drug allergy work-up,[1,2] iRCMs have the peculiarity of being recognized histamine releasers.[27] It should be noted that among patients who presented with a history of anaphylaxis with or without shock, but with an unknown culprit drug and a delay of more than 5 years before testing, the risk of being allergic was not be as high as expected for other drug classes, as shown in patients in clusters 3 to 5.

The predictive and discriminative performance of chronology and clinical history of the index reaction to iRCM have been demonstrated in this study by means of supervised (logistic) and unsupervised (cluster) analyses. The high concordance (>95%) between chronology of the index reaction and that of the positive test result emphasizes the importance of precise clinical history taking. Nevertheless, some discrepancies may occur. These include both imprecise clinical history taking and the (partly justified, partly arbitrary) decision to consider nonimmediate reactions as reactions occurring >1 h after the iRCM administration. Indeed, some patients describing symptoms compatible with delayed anaphylaxis, isolated bronchospasm, or malaise were classified into cluster 1 (non-immediate), and some with MPE with severity signs into an IHR cluster. However, this miss-match is cleared by taking into account in the build-up phase the ST result, ie, patients with MPE and severity signs are attributed to the NIHR cluster (3Pos) and those with isolated anaphylaxis, malaise or bronchospasm in the mixed (IHR and NIHR) 2Pos cluster.

Among the 3 clusters identified in patients with confirmed positive STs, both cluster 1Pos and 3Pos were considered well-defined groups, clearly distinguished by the chronology of the index reaction [IHRs in cluster 1Pos, and NIHRs in cluster 2Pos, and both groups had a shorter delay before testing (2.8 and 5 months, respectively), and all had a known culprit iRCM]. Cluster 2Pos included patients with a longer delay time before testing (median 6 years), and the iRCMs causing the reaction were all unknown.

In a meta-analysis published in 2015,[28] the cross-reactivity rates between iRCMs ranged from 4% to 21% in IHRs, and from 3% to 74% in NIHRs. The underlying mechanisms of cross-reactivities among iRCMs are not fully understood, but iodine is not considered the immune target.[29,30] Our choice was to classify *a priori* iRCMs into 4 subgroups based on chemical structure similarity. The role of cross-reactions between different RCMs has been addressed by previous publications.[1,2,19]

A higher rate of cross-reactivity was shown in clusters 2Pos and 3Pos compared to cluster 1Pos. These 2 clusters accounted for the majority of NIHR (3Pos) or included at least one-third of NIHR (2Pos). This highlights the finding from previous studies that cross-reactivity is more common among NIHR,[6,19] and it encourages the performance of drug allergy work-up with a batterie of iRCM to find appropriate safe alternatives.

We used our previously reported data[6] on reexposure in real-life situations (and not by means of DPT) to a negatively tested iRCM of 233 patients from this cohort in order to see how the population of reexposed and tolerant patients breaks down by cluster. The lowest percentage of reexposed patients per cluster belonged to cluster 2, namely patients with immediate, recent, most likely severe, and well-identified reactions. On the other hand, patients with immediate, but non-severe and remote reactions (cluster 4) accounted for the majority of the reexposed patients per cluster (30%). For immediate reactions (clusters 2–5), a high tolerance (>90%) was observed whatever the cluster. We recognize that the numbers of reexposed patients per cluster are low. Nevertheless, this real-life observation is an important signal

to strengthen the reassurance of patients with immediate reactions relative to subsequent tolerance to an iRCM after negative ST.

Study strengths and limitations

Although retrospective, this study's strenghts include: (i) the large dataset of patients with various clinical histories suggestive of DHR to iRCMs, and with little missing data; (ii) standard operating procedures for medical history questionnaire[31] and allergy work-up with ST at recommended concentrations throughout the past twenty years; and, (iii) original approach with unsupervised analysis. The limitations of this study include: (i) the inclusion of some patients (30 cases) with clinical histories hardly evocative of iRCM DHR; these patients were however tested upon decision of the allergist due to intense symptoms requiring medical intervention at the time of the iRCM injection (cardiac signs: tachycardia, arrythmia; digestive signs: abdominal pain, vomiting; arthralgias); this category only concerned 2% of the studied population; (ii) the often prolonged time between index reaction and ST, bringing about the potential distorsion of the initial clinical history; also, from an immunological point of view, potential loss of sensitivity by ST, as shown for other drugs (nevertheless, the high NPV of ST would argue against this hypothesis) or potential loss of allergy (although this has not been demonstrated to date); (iii) the absence of DPT (although even a positive DPT cannot distinguish specific from non-specific histamine release) (iv) the absence of biological markers, which could be included in the set of arguments for or against a diagnosis of confirmed iRCM allergy; of note, immediate iRCM DHR in the non-allergic group may have occurred through the activation of the MRGPRX2 receptors on mast cells or other non-specific histamine release mechanisms, and this was not addressed, specifically, as a potential variable.

CONCLUSION

In this study, we used unsupervised methods to analyze a population in which allergic reactions occurred in one-tenth of patients tested for DHR to iRCM. Five prototypic clinical phenotypes were distinguished and considered relevant for daily practice. Importantly, this new knowledge can be pragmatically integrated into drug allergy work-up reasoning. Patients with well-defined recent reactions are allergic in up to 17% of cases, but this frequency decreases if reactions are tested more than a decade after their occurrence even if the clinical manifestation resembled anaphylaxis. This separation in itself is highly helpful for clinical decisions in daily practice (especially when the drug allergy work-up cannot be performed, eg an emergency situation), because it allows the allergist to assign clearer risk assessment for patients with very similar clinical pictures (ie, 17% positivity in the well-defined immediate Cluster 2, dropping down by half (8%) in the anaphylactic cluster tested decades after the reaction (Cluster 5), and to 3% in an immediate non-severe cluster (Cluster 4). Thus, encompassing several variables at the same time, this analysis shares a different view on the profiles of the patients we see in our daily activity. By looking deeper into the composition of the clusters, we noticed that patients with a history of an immediate reaction are expected to tolerate reexposure to a ST negative iRCM in >90% of cases regardless of which cluster they are assigned to.

Abbreviations

DPT, Drug provocation test; DHR, Drug hypersensitivity reaction; IHRs, Immediated hypersensitivity reactions; iRCM, iodinated radiocontrast media; NIHRs, Non-immediated hypersensitivity reactions; NPV, Negative predictive value; ST, Skin test.

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Author contributions

WS, TV, AG, PD, and AMC designed the study. WS, AG and TV performed the literature review. WS, NM, RS, and AMC analyzed the data and interpreted the results. WS, TV, and AG drafted the first report. RS, PD and AMC assisted with interpretation and revision of the report. All authors were involved in the review and approval of the manuscript.

Ethics approval

This study was approved by the Institutional Review Boards of the University Hospitals of Montpellier (IRB-MTP 2020–00692). Written informed consents were obtained from study participants at the time of allergy work-up for their anonymous data used for research purposes.

Authors' consent for publication
All authors give consent for the publication.

Data sharing
No additional data available.

Declaration of competing interest
Anca Mirela Chiriac is a consultant for HYCOR biomedical on drug allergy specific IgE dosage. All other authors declare no personal or professional conflicts of interest, and no financial support from the companies that produce and/or distribute the drugs, devices, or materials described in this report.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2022.100680.

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