

## **Abstract.**

**Objectives.** The purpose of the study was to describe the characteristics of patients experiencing hypersensitivity reactions (HRs) to iodinated contrast media (ICM) in a large Italian population and to investigate potential risk factors in order to obtain a risk stratification, helpful in the management of these patients.

**Methods.** Data of 407 patients investigated in 9 Italian Allergy Centers for suspected HRs to ICM were analyzed and compared with a control group of 152 subjects that tolerated one or more ICM-enhanced examinations. The univariate and multivariate logistic regression model was used to evaluate associated factors.

**Results.** The mean age of reactive patients was 61 years and 60% were female; 67% of patients reported immediate reactions and 35% experienced the reaction, more frequently with immediate onset, at the first examination in life. Iomeprol, iopromide and iodixanol were the most frequent culprit agents and 20% of patients showed a positive skin test result. Previous adverse reactions to ICM were reported by 15.6% of patients. The multivariate analysis showed that male gender and age >65 were associated with ICM reactions as protective factors [OR<sub>adj</sub>=0.51; 95%CI: 0.33-0.77 and OR<sub>adj</sub>=0.60; 95%CI: 0.39-0.92 respectively]. Cardio-vascular disease [OR<sub>adj</sub>=2.06; 95%CI: 1.22-3.50], respiratory allergy [OR<sub>adj</sub>=2.30; 95%CI: 1.09-4.83] and adverse drug reactions [OR<sub>adj</sub>=1.99; 95%CI: 1.05-3.77] were identified as risk factors for ICM reactions. Food allergy was not significantly associated with reactions [OR<sub>adj</sub>=1.51; 95%CI: 0.41-5.56].

**Conclusions.** This is the largest study on Italian patients experiencing hypersensitivity reactions to ICM. Most results are in line with other studies, showing some association with factors that could influence the incidence of hypersensitivity reactions but not allowing an easy risk stratification.

**Key words:** Iodinated Contrast media. Risk factors. Drug hypersensitivity. Drug immediate reactions. Drug delayed reactions

**Impact statement:** Characteristics of patients with hypersensitivity reactions to iodinated contrast media are described and compared with subject tolerating the same contrast media allowing to identify some possible risk factors.

## INTRODUCTION.

1 The introduction and increasing use of nonionic low-molecular-weight (LMW) iodinated contrast media (ICM) have  
2 significantly reduced the risk of adverse reactions related to contrast-enhanced radiologic imaging. Hypersensitivity  
3 reactions (HRs) to ICM are rare, but their potential severity represents a cause of concern both for radiologists and for  
4 people who need CM-enhanced radiologic examinations.

5 This could explain the growing interest in the topic in the last 15 years, not only by radiologists but also by allergists  
6 who can give a contribution to knowledge, comprehension and consequently a more correct approach to these reactions  
7 (1-4). For this purpose, the European Network of Drug Allergy (ENDA) published in 2009 the results of a prospective  
8 multicenter study aimed to investigate clinical aspects and a potential allergy work up in this field (5). Although some  
9 areas still remain controversial, as outlined in a recent international consensus, this new perspective has stimulated the  
10 interest to deepen various aspects of the problem (6). Among them, the identification of patients at risk of reaction and  
11 the real utility of the pharmacological premedication are particularly intriguing. The consensus well resumes the  
12 hypothetical risk factors based on the existing studies: while a previous reaction to contrast media is generally accepted  
13 as the main risk factor, the current role of other conditions, such as atopy, asthma, cardiovascular diseases, drug allergy,  
14 female gender, mastocytosis, repeated administrations of ICM, etc., is still uncertain. Nevertheless, these conditions are  
15 often considered in clinical practice, arising fear both in patients and operators. One of the practical consequences is the  
16 abuse of pharmacological premedication by anti-isarines and steroids, without standardized regimes and with  
17 differences not only between allergists and radiologists, but also between the North American and European  
18 recommendations (7,8).

19 To the best of our knowledge, there is no Italian national multicenter study on hypersensitivity reactions to ICM.  
20 Therefore, the main purpose of this study was to investigate the characteristics of patients referred to allergy evaluation  
21 for suspected hypersensitivity reactions to ICM in different Allergy Centers in Italy. The secondary aim was to analyze  
22 possible association between some factors and hypersensitivity reactions to ICM, with the purpose to **identify the**  
23 **possibility** of a risk stratification, a particularly useful tool in adverse drug reactions (ADRs) evaluation (9).

## 24 25 **Methods**

26 This is a retrospective multicenter study approved by the Ethics Committee of the coordinating Center (L'Aquila and  
27 Teramo provinces – Avezzano Hospital- 1/CE/17).

30 *Patients*

31 From 2013 to 2016, in nine Italian Allergy Centers with expertise in drug allergy management, 407 consecutive patients  
32 with hypersensitivity reactions to ICM were analyzed as “reactive group”. Data of 152 consecutive patients from three  
33 Italian Radiologic Centers were collected as “control group” because they tolerated one or more contrast-enhanced  
34 examinations.

35 The following demographic and clinical data were recorded: age, sex, radiological examination, administered ICM,  
36 history of previous exposures, number of examinations in the last year, use of premedication, history of allergy  
37 (inhalant or food allergy) and/or ADRs other than ICM, concomitant cardiovascular diseases, usual anti-hypertensive  
38 medications (i.e. angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor blockers). In the reactive  
39 group, the characteristics of the last adverse reaction and the history of previous ICM reactions, bronchial asthma,  
40 angioedema or mastocytosis were also considered.

41

42 *Clinical Symptoms*

43 In the reactive group, clinical symptom onset was classified in immediate (<1 hour) and non-immediate (>1 hour).  
44 Moreover, the reaction delay was further specified, in order to differentiate very rapid (<10 minutes) and very delayed  
45 (>48 hours) reactions. These data were correlated with the severity of the reaction.

46 Immediate hypersensitivity reactions (IHRs) were classified according to the Ring and Messmer severity scale: grade 1  
47 indicating only cutaneous and/or mucosal symptoms, grade 2 indicating moderate multiorgan involvement with  
48 cutaneous and respiratory or gastrointestinal and/or cardiovascular symptoms, grade 3 including severe life-threatening  
49 multiorgan involvement such as cardiovascular collapse, arrhythmias and bronchospasm, grade 4 with the cardiac  
50 and/or respiratory arrest (10).

51 The non-immediate hypersensitivity reactions (NIHRs) were classified according to the ENDA study in mild, moderate,  
52 and severe (5).

53

54 *Skin tests*

55 As a part of the routine allergy workup, skin tests for the culprit ICM (when known) and for others ICMs commonly  
56 used in Italy were performed in 400 patients. In accordance with the ENDA criteria (5), patients with history of IHR  
57 were analyzed with skin prick test (SPT) and, if negative, with intradermal test (IDT). Patients with clinical history of  
58 NIHR underwent patch test (PT) with reading until 96 hours and, if negative, SPT and IDT. Reactivity to IDT was  
59 evaluated after 20 minutes and during the following 48 hours to detect delayed reactions.

60

61 *Statistical analysis*

62 Continuous variables were expressed as mean and standard deviation, and categorical variables as numbers and  
63 percentages. Data were compared using Student's t- or chi-square tests depending on scale level and distribution.

64 To evaluate factors related to hypersensitivity reactions to ICM, subjects in the reactive group were compared with  
65 subjects in the control group. A logistic regression model was used for univariate analysis with reaction to ICM (yes/no)  
66 as dependent variable and the following factors as independent factors: gender, age in years ( $\leq 65$ ,  $> 65$ ), first exposure  
67 to ICM (yes/no), number of examinations in the last year, premedication (yes/no), cardiovascular disease (yes/no);  
68 number of concomitant pathologies (classes:0;1-2; $\geq 3$ ), respiratory allergy (yes/no), food allergy (yes/no), adverse drug  
69 reactions (yes/no) and anti-hypertensive medications such as ACE-inhibitors (yes/no) and angiotensin receptors  
70 blockers (yes/no).

71 All factors statistically significant by univariate model were included in a multivariate logistic regression analysis  
72 (MLRA). Unadjusted odds ratios (ORs) and adjusted odds ratios (ORadj) with 95% CIs were reported. Significance was  
73 assumed for  $p < 0.05$ . All analysis was performed using STATA 14 software.

74

75 **Results**

76

77 *Characteristics of patients in the reactive group (Table 1)*

78 A total of 274 patients reported IHR (67%: 95%CI: 65%-72%), whereas 133 patients reported NIHR (33%: 95%CI:  
79 28%-37%), 164 patients were males (40%) and the mean age was 61 ( $\pm 14.5$ ) years. Eighty-five % of them were  
80 diagnosed with ICM reactions after a computed tomography (CT) scanning.

81 Premedication had been administered before the radiological examination in 78 patients (19% out of 407) who showed  
82 significantly more frequently a non-immediate rather than an immediate reaction. Among 54 patients with previous  
83 adverse reactions, 42 were premedicated.

84 One hundred twenty-four patients (35% of 351- because of missing data) experienced the reaction during the first ICM-  
85 enhanced examination in their life and significantly more frequently with an immediate rather than delayed onset.

86 Previous reactions to ICM were reported by 54 patients out of 351 (15.4%), without any difference between IHR and  
87 NIHR. Although the suspected culprit agent was known only in about 60% of cases, among the various ICM, iomeprol  
88 and iodixanol were involved in over 50% of the known cases without significant difference between IHR and NIHR.  
89 Moreover, iomeprol was frequently the culprit agent of severe immediate reactions (degree 3 and 4), whereas iodixanol  
90 was responsible significantly more frequently in nonimmediate reactions (16% NIHR vs 3% IHR;  $p < 0.001$ ).

91 In the reactive group, 81 patients reported a history of respiratory and/or food allergy and 86 patients presented  
92 previous ADR to drugs other than ICM. Among patients with respiratory allergy only 26 (36.6%) reported bronchial  
93 asthma.

94 A history of angioedema was present in 2 patients, no cases of mastocytosis were registered.

95

#### 96 *Severity and Time to onset of reaction (Figure 1)*

97 The severity of immediate reactions was classified as follows: grade 1 in 142 (52%) patients, grade 2 in 80 (29%)  
98 patients, grade 3 in 41 (15%) patients and grade 4 in 11 (4%) patients. NIHR were mostly mild (61%) and only one  
99 patient reported a severe nonimmediate reaction diagnosed as DRESS syndrome.

100 Forty-six per cent of immediate reactions (126/271) occurred within ten minutes, and the same rate within 30 minutes.

101 Among the non-immediate reactive group, the reactions were mostly registered within 24 hours (97/130). Only 8.5% of  
102 patients reported reactions over 48 hours after the examination.

103 Figure 1 shows the relation between time of reactions and severity. About half of immediate severe reactions happened  
104 within 10 minutes from the ICM injection.

105

#### 106 *Skin tests*

107 Allergy workup demonstrated at least one positive skin test in 81 patients (20.25% of total enrolled patients): 42  
108 patients were in the IHR group, representing the 15.7% of them, and 39 patients were in the NIHR group, accounting  
109 for the 29.3%. Among patients with history of reaction at their first exposure, 21% showed a positive test.

110 A more detailed description of the results will be the subject of a subsequent paper. .

111

#### 112 *Factors related to ICM reactions (Table II)*

113 In order to evaluate potential risk factors related to ICM hypersensitivity reactions, data of 152 subjects that underwent  
114 an ICM-enhanced CT-scan without any adverse reaction were collected as control group and analyzed.

115 The ICMs used in the control group were the same as in the reactive group (iopamidol in 40%, iomeprol in 32%,  
116 iobitridol in 15%, iohexol in 9%, iodixanol in 4%) with the exception of iopromide and ioversol, never used in the  
117 control group.

118 Collectively, 175 patients reported history of at least one allergy (food allergy, respiratory allergy) and/or ADRs; 150  
119 patients were in the reactive group (37%: 95%CI: 32%-42%) whereas only 26 patients were in the control group (18%:  
120 95%CI: 12%-26%).

121 Univariate analysis between reactive and control group showed a significant association with the following factors: first  
122 exposure (OR=2.2), cardio-vascular diseases (OR=2.1), history of allergy (respiratory: OR=3.0; food: OR=3.3) or ADR  
123 (OR=2.5;). Male gender and age >65 years were protective factors against reactions.

124 The multivariate analysis showed that food allergy was not a significant risk factor associated with reactions:  
125 OR<sub>adj</sub>=1.47 (95%CI: 0.40-5.41), while female gender, age ≤65 years, first ICM exposure, associated cardio-vascular  
126 disease, a history of respiratory allergy and adverse drug reactions were significant risk factors for ICM hypersensitivity  
127 reactions.

128 **(Table III)**

129

130

131 DISCUSSION

132

133 This is the first Italian multicenter study aimed to analyze characteristics and risk factors of patients evaluated for  
134 suspected hypersensitivity reactions to ICM. Demographic characteristics were similar to those of the European  
135 multicenter study (5), with a larger sample size (407 vs 240) and to those of 98 patients in a recent Italian study (11).

136 Thirty-five percent of patients were on their first exposure, showing more frequently an immediate reaction. The  
137 possibility of hypersensitivity reactions to ICM, both immediate and non-immediate, in patients previously unexposed  
138 was already observed, ranging from 13.4% to 50% (11-15). It is usually attributed to a non-immunological  
139 mechanism of action, but some cases show positive skin test with a variable prevalence (35% in ENDA study and 21%  
140 in our study). This seems to suggest a possible previous sensitization through unknown environmental molecules, or  
141 molecules containing carbamoyl side chain (17), or ICM-contaminated drinking water (16).

142 The use of pharmacological premedication was less frequent than expected: specifically, premedication treatment with  
143 either steroids and/or anti-histamines was administered in the majority of cases with a history of previous reactions but  
144 not in the totality of them. The reason why these patients showed more frequently non-immediate reactions is not  
145 clear. One hypothesis is that premedication could be not adequate to prevent late reactions.

146 In our study, the rate of patients with at least one positive skin test (20.25%) is lower than that reported in some studies  
147 (5,12,14) but higher in comparison with others (11, 13), confirming the role of allergy workup in diagnosing and  
148 discriminating between cases with immunological and non-immunological pathogenesis. The time interval between  
149 reaction and evaluation is an important factor influencing the results and could be the reason for the significant more  
150 frequent positivity of test in patients with non-immediate hypersensitivity reactions, less influenced by this factor.

151 Of note, only 16% of our reactive group reported one or more previous ICM adverse reactions. This is described as the  
152 most important risk factor for ICM hypersensitivity reactions, with a variable frequency from 13 to 26 % (5,12). In a  
153 recent study the incidence of HRs was about 20 times higher in patients with a previous history of ICM reactions than in  
154 those without (17).

155 The secondary aim of our study was to evaluate also the role of other potential risk factors related to ICM  
156 hypersensitivity, in order to obtain a risk stratification that may enable a 'delabelling' of low-risk subjects, focusing  
157 attention on high-risk subjects. Literature is rich but inconclusive and sometimes contradictory on this topic (15-19).  
158 Our analysis confirmed the results of other studies about higher risk in female sex (20, 21), age < 65 years and a more  
159 frequent association with cardiovascular diseases (22,23) in the reactive group.

160 Regardless of his endotype, bronchial asthma is often included in the list of risk factors for ICM HRs with an important  
161 difference in the strength of association (OR 2,0 - OR 8,74) (18,19,21). In our study population, the small number of  
162 patients with bronchial asthma did not allow us to correctly analyze this topic. Probably, only uncontrolled asthma has  
163 to be considered a risk factor because it may increase the severity of HR. Such patients are often poor candidates for  
164 receiving contrast, and it is usually avoided by the treating radiologist (24).

165 In line with other studies reporting a prevalence of atopy ranging from 29 up to 50% (5, 11-13), in our reactive group  
166 history of allergy and/or ADRs was present in 37% [95%CI: 32%-42%]. Inhalant allergy (but not asthma) and ADRs  
167 resulted significantly associated with ICM HRs, whereas food allergy was not significantly associated. In literature,  
168 history of concomitant allergy or atopy, with or without a specific disease, is often mentioned as a risk factor, even in  
169 recent studies, reviews, and guidelines (6,9,18,25). The importance of this association should be reduced considering  
170 that this concept seems passively transferred from one review to another, while observational studies usually report only  
171 anamnestic data, not confirmed by diagnostic tests. This is also true for our study where the level of statistical  
172 significance of these results is very low. At the end, this could suggest only a generic predisposing role of other allergic  
173 conditions towards hypersensitivity reactions to ICM.

174 We did not find a significant difference about some factors often reported as a cause of increased risk or increased  
175 severity of anaphylactic reactions such as use of some antihypertensive drugs (21,26) and history of angioedema or  
176 mastocytosis (16), due to the rarity of cases in our study population.

177 Considering the variables related to the examination, in our study a significant difference between reactor and control  
178 subjects seems to indicate that the first exposure of life may represent a risk of reaction. Hypothesis confirmed in the  
179 multivariate analysis and discussed above. Conversely, the number of previous ICM examinations or their frequency is  
180 sometimes indicated among risk factors (18,25). Of note, in our study the number of examinations in the last year

181 before the reaction was significantly greater in the control group compared to the reactive one, probably due to the high  
182 number of oncologic patients, more frequently exposed to ICM-enhanced examinations. This result seems to confirm  
183 the hypothesis of a lower risk in subjects not susceptible who did not react at the first examination (27).

184 A recent Italian document about the management of patients at risk of HRs to contrast media proposes a classification in  
185 which only patients with associated active pathologies such as urticaria-angioedema, mastocytosis, uncontrolled asthma,  
186 history of idiopathic anaphylaxis, and patients with previous reactions to ICMs regardless of their severity, are  
187 considered at increased risk (28). All the other discussed risk factors are considered irrelevant. The future practical use  
188 of these guidelines is needed to confirm whether this is the right way to manage these patients

189

## 190 **Conclusions**

191 This is a multicenter retrospective study on 407 patients evaluated for suspected hypersensitivity reactions to iodinated  
192 contrast media. Characteristics of patients and reactions are in line with other studies coming from different countries.  
193 One of the aims of the study was the evaluation of possible risk factors associated with HRs to ICM in order to obtain a  
194 risk stratification of patients. In summary, our data seem to suggest that these reactions could be the result of multiple  
195 factors acting together with different association in predisposed subjects: age, sex, allergic diseases, cardiovascular  
196 diseases, previous reactions to these agents and features of the contrast examination. This may be the reason for  
197 contradictory results in the literature and for the difficulty in obtaining a valid risk stratification. Among these factors,  
198 our study confirm the risk of reaction, mostly immediate and also with the possibility of severe anaphylaxis, in patients  
199 at their first contrast examination (35% of patients in this study): it deserves great attention among radiologists and  
200 others who administer these drugs. Future research will better clarify the mechanisms and may suggest some corrective  
201 action, for example, to reduce the ICM environmental contamination and consequent sensitization of general population  
202 (29).

203 This study, of course, presents some limitations. First of all, the retrospective design limiting the interpretation of the  
204 results. In fact, the study may be affected by selection and detection bias and the lack of possible investigations about  
205 some concerns. The lack of some data represents a further limitation. Nevertheless, until now, it represents the largest  
206 study on patients with ICM hypersensitivity reactions in Italy. A prospective observational study would better assess  
207 various investigated or not investigated aspects of the topic.

208

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210  
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212 *Conflicts of Interest*  
213  
214 The authors declare that they have no conflicts of interest.

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