Review Article

Contribution of Italian Clinical Research for Contrast Media-Induced Nonrenal Adverse Drug Reactions over the Last Three Decades: A Systematic Review

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Abstract

The aim of this study was to investigate the scientific contribution of Italian clinical research for contrast media-induced nonrenal adverse drug reactions over the last three decades. Ovid Embase, Ovid MEDLINE, Web of Science, and Cochrane Methodology Register were used as data sources to identify Italian descriptive studies, observational studies, meta-analyses, and clinical trials assessing contrast media-induced nonrenal adverse drug reactions as a safety outcome. The population of interest was men and women exposed to a contrast medium. Between 1990 and 2017, 24 original articles investigating contrast-induced nonrenal adverse drug reactions were identified. The cohort study was the most representative study design (10/24; 41.7%). The 24 studies were conducted mainly as monocenter studies (14/24; 58.3%) and without receiving funding (17/24; 70.8%). Seventeen out of 24 studies provided a level of evidence ranging from III-2 (11/24; 45.8%) to IV (6/24; 25.0%) on a Merlin scale. In total, 14 of 24 (58.3%) studies were published in a scientific journal ranked in the first quartile of their subject area. The 24 original articles mainly focused on adverse drug reactions already observed during clinical trials (i.e., idiosyncratic systemic reactions). In conclusion, during the last three decades and a burst was not observed in the Italian clinical research investigating contrast-induced nonrenal adverse drug reactions. High-quality clinical research is needed especially for procedures to prevent the onset of the aforementioned events, to identify risk factors, to minimize the risk of their occurrence, and to optimize their related prognosis.

Keywords: Adverse drug reactions, clinical research, contrast media, humans, Italy

Introduction

Undoubtedly, contrast media are clinically useful due to their ability to enhance medical imaging; however, their use could be associated with a plethora of adverse drug reactions ranging from idiosyncratic systemic reactions (also known as allergy-like reactions or anaphylactoid reactions) to organ-specific reactions (e.g., contrast-induced nephropathy) which could occur within 1 h of contrast medium administration or in days.[1-3] Recently, Sessa *et al.* evidenced a huge interest among Italian researchers in investigating clinical aspects related to contrast-induced nephropathy over the last three decades.[4] However, to date, it is unknown if, in the same period, there was a burst of clinical research investigating contrast-induced nonrenal adverse drug reactions. This should have been expected considering that contrast-induced nonrenal adverse drug reactions have

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a significant negative clinical, humanistic, and economic impact.[5] Moreover, their mechanisms and pathophysiology are still unknown, and that data on well-established risk factors, biomarkers, scores, and their related prognosis are missing.[6-8] In addition, contrast-induced nonrenal adverse drug reactions have been identified mainly during the postmarketing phase in subpopulations typically excluded from clinical trials for which less evidence are available (i.e., contrast-induced thyrotoxicosis in euthyroid patients,[7,8] contrast-induced pulmonary edema in patients with heart failure,[9] contrast-induced extravasation in pediatric and unconscious patients,[10] and contrast-induced nephrogenic fibrosing dermopathy[11]). In this context, providing a clear landscape of state-of-the-art on the contribution of Italian clinical research on methodologies for preventing contrast-induced nonrenal adverse drug reactions, it is crucial to highlight areas that need further improvement. Prevention of contrast-induced adverse drug reactions is among the top priorities of the Italian Society of Radiology, which has edited in April 2018 a joint document for the management, and the prevention of contrast-induced adverse drug reactions in patients undergoing examination with means of contrast (https://www.sirm.org/news/3243). Therefore, to fill this gap in knowledge, we performed a systematic review investigating the scientific contribution of Italian clinical research for contrast-induced nonrenal adverse drug reactions over the last three decades.

Methods

Eligibility criteria

Meta-analyses, clinical trials, and observational studies assessing contrast-induced nonrenal adverse drug reactions as a safety outcome for which at least one author was affiliated with an Italian university/healthcare structure and for which the full text was available in English and/or Italian languages were selected. The reference lists of systematic and not systematic reviews published by Italian authors were included to search for undetected records. We defined a contrast medium as any substance listed in the V08 code of anatomical therapeutic chemical classification as proposed by the World Health Organization. Contrast-induced nonrenal adverse drug reactions were defined as any untoward medical occurrence in a patient administered a contrast medium that not involve the system organ class "renal and urinary disorders" according to the Medical Dictionary for Regulatory Activities.[12]

Outcomes

The main outcome is the narrative overview of the main findings of studies investigating contrast-induced nonrenal adverse drug reaction. Also evaluated was the number of aforementioned studies published per year from 1990 to 2017. Secondary outcomes included: (1) the journal of publication and its related ranking and subject area; (2) the proportion of studies receiving funding; (3) the most representative study design; (4) the level of evidence provided; (5) the proportion of studies with conflict of interest; and (6) collaboration with universities located outside the national territory.

Search strategy

All the manuscript indexed in the period from January 1990 to January 2017 in Ovid MEDLINE, Ovid Embase, and Web of Science as well as those indexed in Cochrane Methodology Register until 2017 were screened. The research strategy and PRISMA checklist are provided in Tables S1 and S2, respectively.

Selection of studies, data extraction, and management

The titles, the abstracts, and the full text were screened by three members of the research team (CR, AM, and MS). If disagreements arose during the evaluation, they were resolved by consensus. When an article was considered eligible to be included in the systematic review, information was extracted according to the data extraction form provided in Table S3. Merlin scale[13] and the SCImago database (http://www.scimagojr.com/) were used to establish the level of evidence of each study, the topic and the ranking of the journal respectively.

Results

Original articles investigating contrast-induced nonrenal adverse drug reactions

Between 1990 and 2017, 24 original articles investigating contrast-induced nonrenal adverse drug reactions were identified [Figures 1 and 2] [Appendices S1-S3]. By evaluating the Italian authors affiliations, the three most representative Italian regions were Lombardia (12/24; 50.0%), Lazio (5/24; 20.8%), and Veneto (4/24; 16.7%). For the 24 studies, the top-three subject area were Pharmacology (6/24; 25.0%), Radiology, Nuclear Medicine and Imaging (5/24; 20.8%), and Cardiology/Cardiovascular Medicine (4/24; 16.7%) [Figure S1]. The cohort study was the most representative study design (10/24; 41.7%) [Figure 3]. The 24 studies were conducted mainly as monocenter studies (14/24; 58.3%) and without receiving funding (17/24; 70.8%). Overall, 75.0% (18/24 studies) had no external collaboration and 87.5% (21/24 studies) did not disclose a conflict of interest [Figures S2 and S3]. Seventeen out of twenty-four studies provided a level of evidence ranging from III-2 (11/24; 45.8%) to IV (6/24; 25.0%) on a Merlin scale [Figure 4]. Six out of twenty-four studies were published in the European Annals of Allergy and Clinical Immunology (2/24; 8.3%), expert opinion on drug safety (2/24; 8.3%), and drug safety (2/24; 8.3%) [Figure S4]. In total, 14 of 24 (58.3%) studies were published in a scientific journal ranked in the first quartile of their subject area [Figure S5].

Head-to-head comparisons

A schematic summary for each study performing a head-to-head comparison among contrast media of the risk of developing contrast-induced nonrenal adverse drug reactions was provided in Appendix S1.

Gadobutrol versus gadoteridol

Anzalone *et al*. compared the efficacy and safety of gadobutrol and gadoteridol in 402 patients

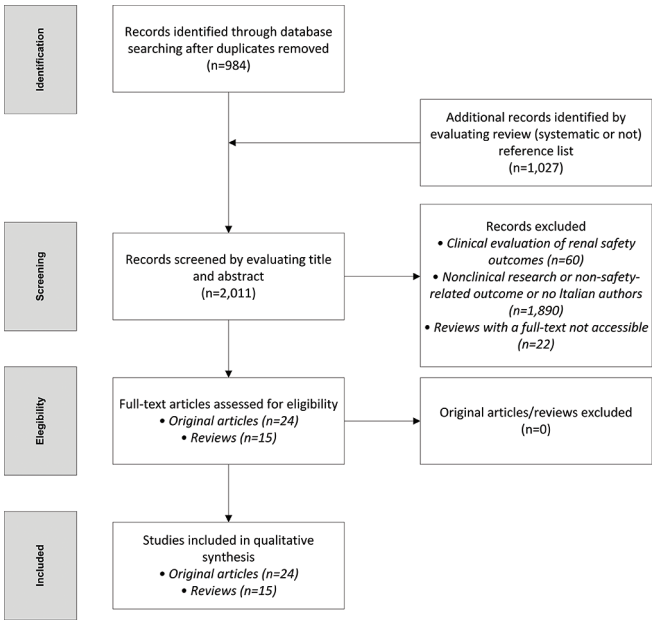

Figure 1: Study flow diagram

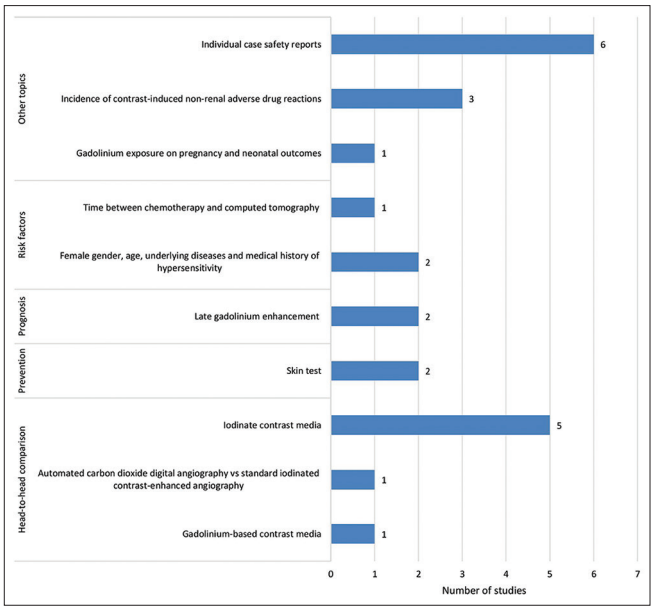

Figure 2: Distribution by topic of the studies included

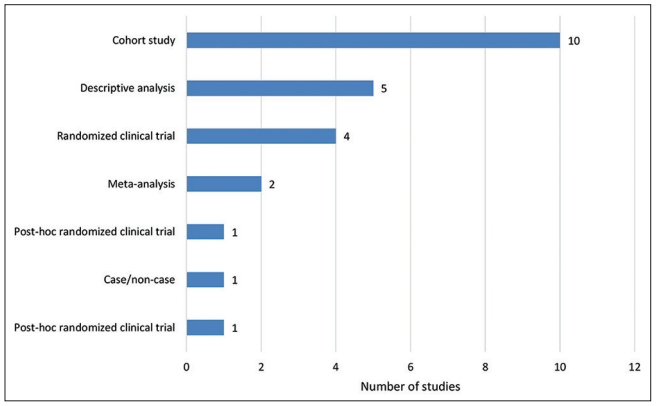

Figure 3: Distribution by the study design of the included studies

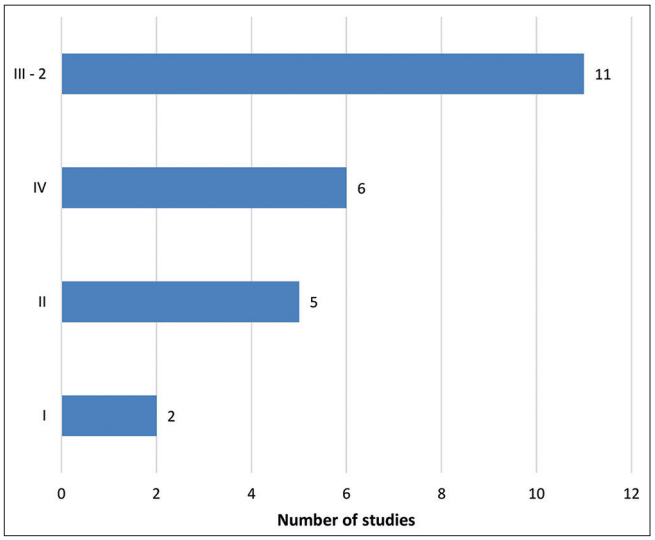

Figure 4: Distribution by the level of evidence provided for the included studies

receiving gadobutrol (228/402; 56.7%) or gadoteridol (174/402; 43.3%) for a magnetic resonance of the central nervous system.[14] The authors found a similar incidence of adverse drug reactions among patients exposed to gadobutrol (10.0%) or gadoteridol (9.7%). The most reported adverse drug reactions were headache, diarrhea, nausea, and dizziness.

Ioxaglate, iopamidol, and iopromide

In 2003, Danzi *et al.* published the results of a study that aimed to compare the impact of ioxaglate (438 patients), iopamidol (442 patients), or iopromide (428 patients) on the risk of developing major adverse cardiac events within 30 days from a coronary intervention.[15] In particular, the authors focused on coronary interventions that involved the use of appropriate antiplatelet agents or new-generation stents. No statistically significant differences were found in the risk of developing major adverse cardiac events among patients exposed to ioxaglate, iopamidol, or iopromide.

Automated carbon dioxide digital angiography versus standard iodinated contrast-enhanced angiography

Scalise *et al*. compared the safety profile of automated carbon dioxide digital angiography for the lower-limb arterial disease to a standard iodixanol-enhanced angiography in 40 patients.[16] Authors found no statistically significant differences in the risk of developing contrast-induced nonrenal adverse drug reactions between the two groups, suggesting this technique with carbon dioxide as a valid alternative for patients at high risk of developing hypersensitivity reactions.

Ioversol versus nonionic iodinated contrast

In 1996, Floriani *et al*. published the results of a meta-analysis of 57 randomized, double-blind clinical trials that aimed to compare the safety profile of ioversol with those of other

nonionic iodinated contrast media.[17] In total, 3854 patients were retrieved from the 57 randomized clinical trials of which 1931 patients were exposed to ioversol and 1923 to the reference. The authors found no statistically significant differences between ioversol and other nonionic contrast media on the risk of developing adverse drug reactions. In both groups, flushing, pain, gastrointestinal disorders, and hematoma were the most frequently occurring adverse drug reactions.

Iomeprol versus iodixanol

In 2009, Romano *et al*. compared the safety profiles of iomeprol and iodixanol in 183 patients (91 exposed to iomeprol and 92 exposed to iodixanol) underwent liver multidetector computed tomography.[18] The authors found that iomeprol had a similar impact on heart rate and on the risk of experiencing adverse drug reactions than iodixanol. The most reported adverse drug reactions were injection site reaction, nausea, vomiting, lymphedema, generalized spasm, and urticaria.

Iomeprol versus iopamidol

In 1994, Beltramello *et al*. published the results of a randomized clinical trial that aimed to assess the efficacy and safety of iomeprol and iopamidol in carotid digital subtraction angiography.[19] The study was conducted in 100 patients of which 50 received iomeprol and 50 received iopamidol. The authors found that no statistically significant differences between the two contrast media for both safety and tolerance parameters. The most detected adverse drug reactions were headache, nausea, and discomfort.

Iomeprol, iopamidol, iopromide, and meglumine sodium diatrizoate

In 1996, Spinazzi *et al*. published the results of a study that aimed to compare differences in the frequency of predictable and unpredictable adverse drug reactions to iomeprol iopamidol, iopromide, and meglumine sodium diatrizoate.[20] The study based on *post hoc* analysis of the results of 26 randomized clinical trials. It involved the following comparison groups: (1) Iomeprol (821 patients) versus iopamidol (754 patients), (2) Iomeprol (404 patients) versus iopromide (408 patients) and (3) Iomeprol (75 patients) versus meglumine sodium diatrizoate (74 patients). The authors found that when iomeprol, iopamidol, iopromide, and meglumine sodium diatrizoate were compared for the risk of developing adverse drug reactions involving the cardiovascular system (e.g., angina pectoris, arrhythmia, hypotension, hypertension, and cardiac arrest), there were no statistically significant differences. However, patients exposed to iopromide or diatrizoate had a higher risk of experiencing adverse drug reactions involving the central nervous system (e.g., convulsion, focal neurologic deficit, and paresthesia).

Studies evaluating risk factors

A schematic summary for each study evaluating risk factors for contrast-induced nonrenal adverse drug reactions was provided in Appendix S1.

Female gender, age, underlying diseases, and medical history of hypersensitivity

In 2008, Lapi *et al*. conducted a study in eight Italian radiology wards to evaluate if physicochemical properties of iodinated contrast media were able to affect the incidence of immediate or delayed adverse drug reactions. The study involved 1514 participants. Monomeric iodinated contrast media had a higher risk of immediate adverse drug reactions (odds ratio [OR] 4.3; 95% confidence interval [CI]: 1.2–15.7) compared to other iodinated contrast media. Adverse drug reactions were predominantly mild or moderate in severity. Moreover, the risk of delayed adverse drug reactions was significantly higher for participants exposed to dimeric contrast media (OR 1.8; 95% CI: 1.1–2.5) than other iodinated contrast media. The female gender was associated with a higher risk of developing contrast-induced delayed adverse drug reactions. Similarly, the young age and the medical history of hypersensitivity reactions to contrast media were associated with a higher risk of developing immediate adverse drug reactions.[21] Similarly, Bartolucci *et al*. conducted a study on 403 patients exposed to iopamidol for urography or dynamic computed tomography to investigate the major risk factors for the development of adverse drug reactions. The incidence of delayed adverse drug reactions among patients exposed to iodinated contrast agents was 50/403 (12.4%). The medical history of allergy, the female gender, the previous exposure to contrast media, and underlying diseases was found as independent predictors for delayed adverse drug reactions. The most frequently reported delayed adverse drug reactions were vomiting, nausea, itching, rash, drowsiness, and headache.[22]

Time between chemotherapy and computed tomography

Farolfi *et al*. investigated the role of time between chemotherapy and computed tomography and the risk of developing acute adverse drug reactions to iodinated contrast media. The study was conducted in 1878 patients with cancer who underwent 3945 contrast-enhanced computed tomography with iomeprol or iobitridol.[23] The authors found that the time between chemotherapy and computed tomography was not a risk factor for developing acute contrast-induced nonrenal adverse drug reactions.

Prognosis of contrast-induced nonrenal adverse drug reactions

A schematic summary for each study evaluating the prognosis of contrast-induced nonrenal adverse drug reactions was provided in Appendix S1.

Late gadolinium enhancement as a prognostic factor for ventricular arrhythmias or cardiac adverse events

Di Marco *et al*. performed a meta-analysis to evaluate the impact of late gadolinium enhancement on the risk of developing ventricular arrhythmias or sudden cardiac death in patients with dilated cardiomyopathy.[24] In total, 29 studies were included enrolling 2948 patients. The authors found that late gadolinium enhancement was associated with a higher risk of developing ventricular arrhythmia or sudden cardiac

death among patients who underwent cardiac magnetic resonance imaging. Similarly, Pedrotti *et al*. assessed the association between late gadolinium enhancement and the risk of developing cardiac adverse events among patients with heart transplantation who underwent cardiac magnetic resonance.[25] The study involved 48 patients. The authors found that patients experiencing late gadolinium enhancement had a higher risk of developing major adverse cardiovascular events or death.

Other topics related to contrast-induced nonrenal adverse drug reactions

A schematic summary for each study evaluating other topics related to contrast-induced nonrenal adverse drug reactions was provided in Appendix S1.

Nonrenal adverse drug reactions with the off-label use of gadolinium-based contrast media

In 2015 Lombardi *et al*., published the results of a multi-national study involving 57 European centers for a total of 37,788 patients from the EuroCRM Registry[26] that aimed to assess the incidence of adverse drug reactions during an off-label use of gadolinium-based contrast media for cardiovascular magnetic resonance. The authors found that the incidence of adverse drug reactions was 0.12% (45 adverse drug reaction out of 37,788 doses of contrast media administered). Adverse drug reactions were mainly mild in severity (nausea, rashes, and hives).

Contrast-induced neurotoxicity

In 2013, Kocabay *et al*. published the results of a study that aimed to investigate contrast-induced neurotoxicity among patients undergoing coronary angiography.[27] The study was conducted in 6000 patients exposed to iopromide and overall, nine patients developed neurotoxicity. Major signs and symptoms included confusion, ophthalmoplegia, monoplegia, and cerebellar dysfunction.

Contrast-induced nonrenal adverse drug reactions during fluorescein administration

In 2008, Felisati *et al*. published the preliminary results of a multicenter study investigating the efficacy and safety of fluorescein administration for craniosinusal fistulae. Fluorescein was administrated to 53 patients and the authors reported that no adverse drug reactions were observed both when fluorescein was used at a dose ≤50 mg for diagnostic purposes (six cases) and at dosage for therapeutic purposes (47 cases).[28]

Impact of gadolinium exposure on pregnancy and neonatal outcomes

In 2007, De Santis *et al.* evaluated the impact of gadolinium exposure on pregnancy and neonatal outcomes. The study was conducted on 26 pregnant women exposed to gadopentetate dimeglumine during the first trimester of pregnancy.[29] In one case, it was found a congenital anomaly at birth. In particular, the newborn had two hemangiomas. In addition, in two cases, it was found two pregnancies complicated by miscarriage.

Skin test and breakthrough reactions to iodinated contrast media

In 2016, Berti *et al.* evaluated the rate of positive skin test among patients that experienced breakthrough reactions to iodinated contrast media.[30] The study was conducted on 35 patients with prior breakthrough hypersensitivity reactions in comparison to a control group that experienced hypersensitivity reaction without premedication. The authors found that patients with prior breakthrough reactions have statistically significant lower immunologically proven positive skin test to iodinated contrast media compared to patients with hypersensitivity reactions. These results suggest that a considerable fraction of breakthrough reactions to iodinated contrast media could be nonallergic hypersensitivity reactions that could not be prevented by a proper, well-timed skin testing.

Individual case safety reports

Naldi *et al*. investigated individual case safety reports reporting contrast-induced cutaneous adverse drug reactions among those sent through spontaneous reporting systems of four Italian Regions.[31] Overall, 71 cases reporting cutaneous adverse drug reactions (mainly exanthema or urticaria) with a plausible causal relationship with the administration of a contrast medium were found. Similarly, in 2007, Cutroneo *et al*. published the results of a descriptive analysis of individual case safety reports that reported contrast media as suspected drugs among those sent through Sicily Region (Italy) spontaneous reporting system. The author found 100 cases involving contrast media, mainly occurred during computed axial tomography (63/100 cases). The most reported adverse events were erythema, urticaria, vomiting, and generalized skin rash. The study investigated both gadolinium-based and iodinated contrast media.[32] In 2015[33] and 2016,[34] Sessa *et al*. performed two descriptive studies on individual case safety reports reporting contrast media as suspected drug among those sent through Campania Region (Italy) spontaneous reporting system. The top-three most reported contrast media were iopamidol, gadobenic acid, and gadoteric acid. The majority of cases reported hypersensitivity reactions as adverse drug reaction; in seven cases, adverse drug reactions were preventable. In particular, in two cases, there were pharmacokinetic and/or pharmacodynamic interactions between the contrast media and co-administrated drugs and in five cases, radiologists did not administer appropriate preventive measures. In 2005[35] and 2008,[36] Leone *et al*. presented the results of two studies that aimed to evaluate the impact of drug-related deaths and drug-induced anaphylaxis. The authors found that between January 2001 and December 2006, in total, 26 cases of death occurred following the administration of contrast media. The majority of cases described the cause of death as related to the development of immediate allergy-like reactions. Regarding the drug-induced anaphylaxis, the authors found that when compared to other drug classes, contrast media had a reporting OR of 7.26 (95% CI: 5.79, 9.11).

Discussion

This study is part of a set of initiatives promoted by Campania Pharmacovigilance and Pharmacoepidemiology Regional Centre over the last few years.[4,34,37-60] Unexpectedly, during the last three decades, a burst was not observed in the Italian clinical research investigating contrast-induced nonrenal adverse drug reactions. In fact, based on our research strategy, only 24 clinical studies have been identified from 1990 to 2017. This result is in contrast with those assessed by Sessa *et al*. for contrast-induced nephropathy over the same period and the same research strategy, and it is, in our opinion, unjustified given the frequency and the clinical impact of contrast-induced nonrenal adverse drug reactions.[4] In fact, these adverse drug reactions could result in death[61,62] and the costs for their clinical management are not negligible.[63] An example of the high frequency and the clinical impact of contrast-induced nonrenal adverse drug reactions could be provided with acute idiosyncratic systemic reactions that are unpredictable but potentially preventable since nonrenal adverse drug reactions could occur within 60 min of contrast medium administration.[8] Acute idiosyncratic systemic reactions include potentially life-threatening reactions such as laryngeal edema, vasovagal reactions, cardio-respiratory arrest, hypotensive shock, and convulsions.[8] For iodinated contrast agents, the rate of acute idiosyncratic systemic adverse drug reactions was assessed to be 5%–12% for those contrast agents with high osmolality, of which those mild and severe with a rate of 1%–2% and 0.10%–0.15%, respectively, which resulted from four to five times lower with that of low osmolality iodinated contrast agents.[10,64,65] This means that for iodinated contrast media with a high osmolality for each 1000 contrast media administrations, 50–120 adverse drug reactions could be expected, of which 10 or 20 moderate acute events and one severe acute event. For late adverse drug reactions to iodinated contrast media, instead, the rate has been reported to be between 0.52% and 23%, mostly reported as headache, skin-related disorders, and gastrointestinal disturbances.[22] For gadolinium-based contrast media, it has been established that acute severe, life-threatening idiosyncratic systemic reactions occur in between 1 in 10,000 and 1 in 300,000.[66] Based on these estimations, the expected magnitude of the Italian population potentially at risk of developing this type of contrast-induced nonrenal adverse drug reactions is massive. In fact, it should be mentioned that the Italian Society of Radiology has recently declared that each year, in Italy, radiologist performed 100,000,000 examination with an increasing trend for radiological examination (+31%), computed tomography (+107%), and pediatric examination (+378%) in the last 7 years and an increased trend of usage of iodinate contrast media.[67] Among our results, even more surprising, it was the finding that only 5/24 (20.8%) studies investigated procedures to prevent contrast-induced nonrenal adverse drug reactions or aimed to identify risk factors for their development. In particular, only two studies investigated the role of skin testing as preventative measures for idiosyncratic systemic reactions for which, previous studies have clearly evidenced that this test is not useful for minimizing the risk of idiosyncratic systemic reactions. In this regard, we believe that especially for preventive measures and risk factors for contrast-induced nonrenal adverse drug reactions, more clinical research is needed. Open questions exist on the clinical usefulness of premedication in specific subpopulations, such as, for example, high-risk patients and its effectiveness for moderate or severe reactions.[68] Still unresolved doubt exists on the possible role as risk factors for several diseases, such as, for example, myasthenia gravis and pheochromocytoma for which further investigation is necessary.[68] Another surprising result in our systematic review is the high proportion of studies focusing on adverse drug reactions mainly observed during clinical trials (mainly idiosyncratic systemic reactions) and the scarce interest given to adverse drug reactions mainly occurring during postmarketing surveillance such as gadolinium-induced nephrogenic systemic fibrosis and gadolinium cerebral accumulation.[66,69] In fact, while communications from regulatory agencies for gadolinium cerebral accumulation were more recent,[70] the first clinical study investigating the relationship between gadolinium and nephrogenic systemic fibrosis was published in 2006.[66] For both topics, still exists the unresolved question on the best procedures to prevent the onset of aforementioned events, which risk factors promote their onset, and how to optimize their related prognosis. Finally, in contrast with the study conducted by Sessa *et al.* which found that clinical research for contrast-induced nephropathy was mainly conducted by cardiologists, for the 24 studies included in our systematic review, the top-two subjects area were Pharmacology (6/24; 25.0%) and Radiology/Nuclear Medicine/Imaging (5/24; 20.8%). While for percutaneous coronary arteriography radiologists have mainly demonstrated marginal interest, they remain the cornerstone for other radiological examinations and its related research. In fact, it should be mentioned that despite few studies were published from 1990 to 2017 more than 20.0% of them were published in a scientific journal ranked in the first quartile of their subject area although they were able to provide evidence ranging from III-2 to IV on a Merlin scale.

Conclusion

This study found a potential for improving Italian research on contrast-induced nonrenal adverse drug reactions given that only a few studies have been found in the period 1990–2017. Clinical research is needed, especially for procedures to prevent the onset of aforementioned events, to identify risk factors, to minimize the risk of their occurrence, and to optimize their related prognosis.

Compliance with Ethical Standards

Ethical approval

This article does not contain any studies with human participants performed by any of the authors.

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Conflicts of interest

There are no conflicts of interest.

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S1 Appendix: Meta-analyses, observational studies, and clinical trials assessing contrast-induced nonrenal adverse events as clinical outcome for which were involved Italian researchers among those published from January 1990 to January 2017 in the scientific literature

Anzalone 2014[14]	
List of elements	**Value**
ID	1
Year of publication	2015
Italian region/s involved	Lombardia
The title of the manuscript	Safety and efficacy of gadobutrol for contrast-enhanced magnetic resonance imaging of the central nervous system: Results from a multicenter, double-blind, randomized, comparator study
Study design	Randomized clinical trial
Mono-/multi-center	Multi-center
The level of evidence	II
Funding	Yes
Conflict of interest	Yes
External collaboration	Yes
Journal	Magnetic Resonance Insights
Topic	Radiology, Nuclear Medicine And Imaging
Ranking	123
Danzi *et al*., 2003[15]	
ID	2
Year of publication	2003
Italian region/s involved	Lombardia
The title of the manuscript	Nonionic low-osmolar contrast media have no impact on major adverse cardiac events in patients undergoing coronary stenting with appropriate antiplatelet therapy
Study design	Randomized clinical trial
Mono-/multi-center	Mono-center
The level of evidence	II
Funding	No
Conflict of interest	No
External collaboration	No
Journal	Catheterization and Cardiovascular Interventions
Topic	Cardiology and Cardiovascular Medicine Radiology, Nuclear Medicine and Imaging
Ranking	63
Scalise *et al*., 2015[16]	
ID	3
Year of publication	2015
Italian region/s involved	Lombardia, Emilia Romagna
The title of the manuscript	Automated carbon dioxide digital angiography for lower-limb arterial disease evaluation: Safety assessment and comparison with standard iodinated contrast media angiography
Study design	Cohort study
Mono-/multi-center	Mono-center
The level of evidence	III - 2
Funding	No
Conflict of interest	No
External collaboration	No
Journal	Journal of Invasive Cardiology
Topic	Cardiology and Cardiovascular Medicine
Ranking	148
Floriani *et al*., 1996[17]	
ID	4
Year of publication	1996

Contd...

S1 Appendix: Contd...

Floriani *et al*., 1996[17]	
Italian region/s involved	Lombardia
The title of the manuscript	Clinical profile of ioversol. A meta-analysis of 57 randomized, double-blind clinical trials
Study design	Meta-analysis
Mono-/Multi-center	-
The level of evidence	I
Funding	No
Conflict of interest	No
External collaboration	Yes
Journal	Investigative Radiology
Topic	Radiology, Nuclear Medicine, And Imaging
Ranking	7
Romano *et al*., 2009[18]	
ID	5
Year of publication	2009
Italian region/s involved	Campania, Lazio, Lombardia
The title of the manuscript	Enhancement and safety of iomeprol-400 and iodixanol-320 in patients undergoing abdominal multidetector CT
Study design	Randomized clinical trial
Mono-/multi-center	Multi-center
The level of evidence	II
Funding	No
Conflict of interest	No
External collaboration	Yes
Journal	British Journal of Radiology
Topic	Medicine (miscellaneous)
Ranking	384
Beltramello *et al*., 1994[19]	
ID	6
Year of publication	1994
Italian region/s involved	Veneto
The title of the manuscript	Double-blind comparison of safety and efficacy of iomeprol and iopamidol in carotid digital subtraction angiography
Study design	Randomized clinical trial
Mono-/multi-center	Mono-center
The level of evidence	II
Funding	No
Conflict of interest	No
External collaboration	No
Journal	European Journal of Radiology
Topic	Radiology, Nuclear Medicine, and Imaging
Ranking	44
Spinazzi *et al*., 1996[20]	
ID	7
Year of publication	1996
Italian region/s involved	Lombardia
The title of the manuscript	Predictable and unpredictable adverse reactions to uroangiographic contrast media
Study design	*Post hoc* analysis randomized clinical trial
Mono-/multi-center	Mono-center
The level of evidence	II
Funding	No
Conflict of interest	Yes

Contd...

S1 Appendix: Contd...

Spinazzi *et al*., 1996[20]	
External collaboration	No
Journal	Academic Radiology
Topic	Radiology, Nuclear Medicine, And Imaging
Ranking	56
Lapi *et al*., 2008[21]	
ID	8
Year of publication	2008
Italian region/s involved	Toscana, Lazio
The title of the manuscript	Safety aspects of iodinated contrast media related to their physicochemical properties: A pharmacoepidemiology study in two Tuscany hospitals
Study design	Cohort study
Mono-/multi-center	Multi-center
The level of evidence	III - 2
Funding	Yes
Conflict of interest	No
External collaboration	No
Journal	European Journal of Clinical Pharmacology
Topic	Pharmacology (medical)
Ranking	56
Bartolucci *et al*., 2000[22]	
ID	9
Year of publication	2000
Italian region/s involved	Lazio
The title of the manuscript	Late reactions to a radiologic contrast media (Iopamidol-Bracco). Prospective study
Study design	Cohort study
Mono-/multi-center	Mono-center
The level of evidence	III - 2
Funding	No
Conflict of interest	No
External collaboration	No
Journal	La Radiologia Medica
Topic	Radiology, Nuclear Medicine, And Imaging
Ranking	102
Farolfi *et al*., 2014[23]	
ID	10
Year of publication	2014
Italian region/s involved	Emilia Romagna
The title of the manuscript	Does the time between CT scan and chemotherapy increase the risk of acute adverse reactions to iodinated contrast media in cancer patients?
Study design	Cohort study
Mono-/multi-center	Mono-center
The level of evidence	III - 2
Funding	No
Conflict of interest	No
External collaboration	No
Journal	BMC cancer
Topic	Biochemistry, Genetics and Molecular Biology
Ranking	421

Contd...

S1 Appendix: Contd...

Di Marco *et al*., 2017[24]	
ID	11
Year of publication	2017
Italian region/s involved	Toscana
The title of the manuscript	Late gadolinium enhancement and the risk of ventricular arrhythmias or sudden death in dilated cardiomyopathy: Systematic review and meta-analysis
Study design	Meta-analysis
Mono-/multi-center	-
The level of evidence	I
Funding	Yes
Conflict of interest	Yes
External collaboration	Yes
Journal	JACC: Heart Failure
Topic	Cardiology and Cardiovascular Medicine
Ranking	6
Pedrotti *et al*., 2017[25]	
ID	12
Year of publication	2017
Italian region/s involved	Lombardia
The title of the manuscript	Prognostic impact of late gadolinium enhancement in the risk stratification of heart transplant patients
Study design	Cohort study
Mono-/multi-center	Mono-center
The level of evidence	III - 2
Funding	Yes
Conflict of interest	No
External collaboration	No
Journal	European Heart Journal
Topic	Cardiology and Cardiovascular Medicine
Ranking	3
Lombardi 2015[26]	
ID	13
Year of publication	2015
Italian region/s involved	Toscana
The title of the manuscript	2015 Update on acute adverse reactions to gadolinium based contrast agents in cardiovascular MR. Large Multi-National and Multi-Ethnical Population Experience with 37,788 Patients from the EuroCMR Registry
Study design	Cohort study
Mono-/multi-center	Multi-center
The level of evidence	III - 2
Funding	Yes
Conflict of interest	No
External collaboration	Yes
Journal	Journal of Cardiovascular Magnetic Resonance
Topic	Radiological and Ultrasound Technology
Ranking	1
Kocabay *et al*., 2013[27]	
ID	14
Year of publication	2013
Italian region/s involved	Veneto
The title of the manuscript	Contrast-induced neurotoxicity after coronary angiography

Contd...

S1 Appendix: Contd...

Kocabay *et al*., 2013[27]	
Study design	Cohort study
Mono-/multi-center	Mono-center
The level of evidence	III - 2
Funding	No
Conflict of interest	No
External collaboration	Yes
Journal	Journal of the American College of Cardiology
Topic	Cardiology and cardiovascular medicine
Ranking	222
Felisati *et al*., 2008[28]	
ID	15
Year of publication	2008
Italian region/s involved	Lombardia
The title of the manuscript	Italian multicentre study on intrathecal fluorescein for craniosinusal fistulae
Study design	Cohort study
Mono-/multi-center	Multi-center
The level of evidence	III - 2
Funding	No
Conflict of interest	No
External collaboration	No
Journal	Acta otorhinolaryngologica Italica
Topic	Otorhinolaryngology
Ranking	40
De Santis *et al*., 2007[29]	
ID	16
Year of publication	2007
Italian region/s involved	Lazio
The title of the manuscript	Gadolinium periconceptional exposure: Pregnancy and neonatal outcome
Study design	Descriptive analysis
Mono-/multi-center	Cohort study
The level of evidence	III - 2
Funding	No
Conflict of interest	No
External collaboration	No
Journal	Acta Obstetricia et Gynecologica Scandinavica
Topic	Obstetrics and Gynecology
Ranking	28
Berti *et al*., 2016[30]	
ID	17
Year of publication	2016
Italian region/s involved	Lombardia, Liguria
The title of the manuscript	Patients with breakthrough reactions to iodinated contrast media have low incidence of positive skin tests
Study design	Case-control
Mono-/multi-center	Mono-center
The level of evidence	III - 2
Outcome	To evaluate the rate of positive skin test among patients with previous breakthrough reactions to iodinated contrast media
Funding	No
Conflict of interest	No
External collaboration	No

Contd...

S1 Appendix: Contd...

Berti *et al*., 2016[30]	
Journal	European Annals of Allergy and Clinical Immunology
Topic	Immunology and Allergy
Ranking	144 (q3)
Della Torre 2015[65]	
ID	18
Year of publication	2015
Italian region/s involved	Lombardia, Liguria
The title of the manuscript	Proposal of skin tests based approach for the prevention of recurrent hypersensitivity reactions to iodinated contrast media
Study design	Cohort study
Mono-/multi-center	Mono-center
The level of evidence	III - 2
Funding	No
Conflict of interest	No
External collaboration	No
Journal	European Annals of Allergy and Clinical Immunology
Topic	Immunology and Allergy
Ranking	144
Naldi *et al*., 1998[31]	
ID	19
Year of publication	1998
Italian region/s involved	Lombardia, Veneto, Friuli Venezia Giulia, Sicilia
The title of the manuscript	Cutaneous reactions to drugs. An analysis of spontaneous reports in four Italian regions
Study design	Descriptive analysis
Mono-/multi-center	Multi-center
The level of evidence	IV
Funding	No
Conflict of interest	No
External collaboration	No
Journal	British Journal of Clinical Pharmacology
Topic	Pharmacology (medical)
Ranking	28
Cutroneo *et al*., 2007[32]	
ID	20
Year of publication	2007
Italian region/s involved	Sicilia
The title of the manuscript	Adverse reactions to contrast media: An analysis of spontaneous reporting data
Study design	Descriptive analysis
Mono-/multi-center	Mono-center
The level of evidence	IV
Funding	Yes
Conflict of interest	No
External collaboration	No
Journal	Pharmacological research
Topic	Pharmacology, Toxicology, and Pharmaceutics
Ranking	37
Sessa *et al*., 2015[33]	
ID	21
Year of publication	2015

Contd...

S1 Appendix: Contd...

Sessa *et al*., 2015[33]	
Italian region/s involved	Campania
The title of the manuscript	Suspected adverse reactions to contrast media in Campania Region (Italy): Results from 14 years of postmarketing surveillance
Study design	Descriptive analysis
Mono-/multi-center	Mono-center
The level of evidence	IV
Funding	No
Conflict of interest	No
External collaboration	No
Journal	Expert opinion on drug safety
Topic	Pharmacology (medical)
Ranking	39
Sessa *et al*., 2016 [34]	
ID	22
Year of publication	2016
Italian region/s involved	Campania
The title of the manuscript	Campania preventability assessment committee: A focus on the preventability of the contrast media adverse drug reactions
Study design	Descriptive analysis
Mono-/multi-center	Mono-center
The level of evidence	IV
Funding	Yes
Conflict of interest	No
External collaboration	No
Journal	Expert opinion on drug safety
Topic	Pharmacology (medical)
Ranking	39
Leone *et al*., 2005[35]	
ID	23
Year of publication	2005
Italian region/s involved	Veneto, Lombardia, Emilia Romagna
The title of the manuscript	Drug-induced anaphylaxis. Case/noncase study based on an Italian pharmacovigilance database
Study design	Case/noncase study
Mono-/multi-center	Multi-center
The level of evidence	IV
Funding	No
Conflict of interest	No
External collaboration	No
Journal	Drug safety
Topic	Pharmacology (medical)
Ranking	36
Leone *et al*., 2008[36]	
ID	24
Year of publication	2008
Italian region/s involved	Veneto, Lazio
The title of the manuscript	Drug-related deaths. An analysis of the Italian spontaneous reporting database
Study design	Descriptive analysis
Mono-/multi-center	Multi-center
The level of evidence	IV
Funding	No

Contd...

S1 Appendix: Contd...

	Leone *et al*., 2008[36]
Conflict of interest	No
External collaboration	No
Journal	Drug safety
Topic	Pharmacology (medical)
Ranking	36

MR=Magnetic resonance, CT=Computed tomography, CMR=Cardiovascular MR, BMC=BioMedCentral

S2 Appendix: Review Included

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S3 Appendix: Full-texts Not Accessible

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