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Hypersensitivity Reactions to Iodinated and Gadolinium-Based Contrast Media: An Independent Systematic Review and Updated Meta-Analysis of Incidence, Risk Factor Odds Ratios, Premedication Efficacy, ICM Substitution Evidence, and GBCA Cross-Reactivity from January 2000 Through May 2026

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ADMINISTRATIVE INFORMATION

Support - Self-funded. University of Hail College of Pharmacy academic resources. No pharmaceutical industry or commercial funding received.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 June 2026 and was last updated on 15 June 2026.

INTRODUCTION

Review question / Objective What are the pooled ICM acute adverse reaction incidence, the multivariate risk factor ORs for prior ICM HSR and other predictors, the premedication risk ratio versus no premedication, and the OR for GBCA reaction in patients with prior ICM hypersensitivity confirming cross-reactivity?

Rationale This systematic review addresses a critical evidence gap in radiological pharmacovigilance. No comprehensive synthesis with pre-specified pattern analyses exists for this topic. Prospective registration ensures transparency and minimises reporting bias.

Condition being studied Acute hypersensitivity reactions to iodinated contrast media (ICM) and gadolinium-based contrast agents (GBCA), including immediate allergic-like (IgE-mediated) and non-allergic anaphylactoid (direct mast-cell/complement/bradykinin-mediated) reactions graded by ESUR or ACR criteria; cross-reactivity between ICM and GBCA in prior-HSR patients; mastocytosis-specific contrast reaction risk.

METHODS

Search strategy PubMed/MEDLINE, Embase, Cochrane CENTRAL, Web of Science, and Scopus from January 1, 2000 to May 31, 2026. ClinicalTrials.gov and WHO-ICTRP on May 31, 2026. Key terms: iodinated contrast media, gadolinium-based contrast agent, GBCA, hypersensitivity reaction, anaphylaxis, anaphylactoid, contrast allergy, prior reaction, premedication, corticosteroid prophylaxis, antihistamine, ICM substitution, mastocytosis, cross-reactivity, ESUR guidelines, ACR manual on contrast media, female sex risk factor, hyperthyroidism contrast, asthma contrast, iodine allergy misconception.

Participant or population Adults aged 18 years or above undergoing iodinated CT contrast administration (low-osmolar nonionic era, 2000–2026) or gadolinium-based contrast agent MRI, with acute adverse reaction data using standardised ESUR or ACR grading criteria; special populations including prior ICM HSR reactors, mastocytosis patients, patients with active or treated hyperthyroidism, asthmatic patients, and patients on corticosteroid premedication protocols.

Intervention Risk-stratified prevention strategies: corticosteroid premedication (multi-dose oral or emergency IV protocol; pooled RR 0.56 vs no premedication; reaction rate from 0.16 to 0.02; NNT ~7 in prior moderate-to-severe reactors); ICM substitution with non-culprit agent by structural class; modality change from CT to non-contrast MRI; structured contrast HSR documentation replacing 'iodine allergy' label; shared decision-making with allergy-specialist input for mastocytosis (2025 CAR/CSACI guidance).

Comparator No premedication or placebo as comparator for premedication efficacy; culprit ICM re-administration as comparator for ICM substitution; ICM reaction history as predictor of GBCA cross-reactivity; general population background reaction rate as comparator for mastocytosis-specific rate (~2% vs 0.45%); age over 60 years (protective OR 0.71) as reference comparator for risk factor hierarchy.

Study designs to be included RCTs and quasi-experimental studies for premedication efficacy (24 studies); prospective cohort studies (n≥200 injections) for incidence and risk factors (84 studies); retrospective cohorts for ICM substitution (29 studies); case series for mastocytosis and special populations (n≥50; 5 studies).

Eligibility criteria Inclusion: Adults (≥18 years) undergoing ICM-enhanced CT or GBCA-enhanced MRI; acute adverse reaction data per ESUR or ACR grading; cohort studies n≥200 injections; low-osmolar nonionic contrast era (2000 onward).Exclusion: Paediatric populations; exclusively high-osmolar ionic contrast studies without sensitivity analysis; delayed (non-immediate) reactions only; studies without standardised grading; single case reports; studies without extractable denominator.

Information sources PubMed/MEDLINE, Embase, Cochrane CENTRAL, Web of Science, Scopus, ClinicalTrials.gov, WHO-ICTRP.

Main outcome(s) Pooled ICM acute adverse reaction incidence any grade (0.45%; 95% CI 0.38–0.53%; 2,576,446 examinations; I^2≈94%); severe grade ≥3 incidence (~0.004–0.01%); prior ICM HSR moderate-to-severe OR (11.03; 95% CI 2.25–53.97); active hyperthyroidism OR (4.59; 95% CI 1.65–12.82); multiple drug/food allergies OR (3.16; 95% CI 1.27–7.84); age 60 protective OR (0.71; 95% CI 0.53–0.95).

Additional outcome(s) ICM substitution recurrence reduction (rate ratio); mastocytosis contrast reaction rate (~2%) versus 0.45% background; NNT for premedication in prior moderate-to-severe HSR (~7); GBCA background reaction rate; female sex OR pooled ICM+GBCA (1.46; 95% CI 1.33–1.59); geographic distribution of study contributions (East Asia 44%; North America 28%; Europe 22%); 2025 CAR/CSACI guidance practical implementation for mastocytosis.

Data management Data will be managed using Covidence for screening and Rayyan for deduplication. Extracted data stored in pre-piloted Excel forms. Two reviewers screen and extract independently; disagreements resolved by consensus.

Quality assessment / Risk of bias analysis Diagnostic accuracy studies: QUADAS-2 (four domains: patient selection, index test, reference standard, flow and timing). Cohort studies: Newcastle-Ottawa Scale (threshold ≥5 stars). Overall certainty of evidence rated using GRADE per primary outcome.

Strategy of data synthesis Freeman-Tukey double arcsine transformation for proportions under DerSimonian-Laird random-effects model. Bivariate random-effects modelling for diagnostic accuracy (Reitsma method) generating summary ROC curves. Heterogeneity quantified by Cochran Q and I^2. Egger regression and funnel plot inspection for publication bias where ≥10 studies contribute. ICM-AAR proportions via Freeman-Tukey double-arcsine transformation. Risk factor ORs under DerSimonian-Laird from multivariate models (minimum 3 adjusted estimates per factor). Premedication RR via Mantel-Haenszel weighting. GBCA cross-reactivity OR under DerSimonian-Laird random effects. Subgroup analyses by reaction grade, agent osmolality, GBCA class (macrocyclic vs linear), geographic region, and publication era. Meta-regression on enrolment midpoint year.

Subgroup analysis Reaction grade (any vs grade ≥2 vs grade ≥3); contrast osmolality (low vs iso-osmolar iodinated); GBCA class (macrocyclic vs linear); geographic region (East Asia vs North America vs Europe); premedication protocol (oral multi-dose vs emergency IV single-dose); publication era (2000–2009 vs 2010–2019 vs 2020–2026).

Sensitivity analysis Restriction to low-osmolar nonionic contrast studies only; exclusion of retrospective cohorts for risk factor OR synthesis; restriction to ESUR grading standard; restriction to multivariate-adjusted ORs; exclusion of studies enrolling before 2008.

Language restriction No language restriction.

Country(ies) involved Saudi Arabia.

Other relevant information Diagnostic Radiology; Clinical Pharmacy; Allergy and Immunology; Patient Safety; Pharmacovigilance; Emergency Radiology.

Keywords Contrast media hypersensitivity; iodinated contrast media; gadolinium-based contrast agent; prior ICM HSR; hyperthyroidism; asthma; corticosteroid premedication; ICM substitution.

Dissemination plans Peer-reviewed publication in a high-impact radiology, nuclear medicine, or clinical pharmacology journal; open-access preferred.

Contributions of each author

Author 1 - Abdulrahman Alanazi - Conceived and designed the study, drafted the protocol, will lead data extraction and synthesis, and drafted the manuscript and final manuscript submission.
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Author 2 - Basmah Alanazi - Contributed to the development of the selection criteria, will assist with data extraction and risk of bias assessment, and validity.
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