

Original article

Breakthrough allergic-like reactions to contrast media despite preventive measures in patients with prior reactions: A retrospective study

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Abstract

Background: Breakthrough allergic-like reaction (BTR) to iodinated contrast media, an allergic-like reaction despite premedication and contrast switching, remains an important safety concern.

Objective: To determine BTR incidence and identify its predictors, particularly whether contrast group membership and side-chain similarity are associated with reaction risk.

Methods: A retrospective cohort study of iodinated contrast media administration with premedication in patients with prior allergic-like reactions at Bangkok Metropolitan Administration General Hospital (September 2015–December 2025). The primary outcome was BTR incidence. Contrast administration was classified into three categories: 1) different group, different side chain; 2) different group, similar side chain; and 3) same group, same side chain. Generalized estimating equations (GEE) was used to account for multiple exposures per patient.

Results: A total of 572 contrast administrations from 210 patients were included; BTR occurred in 55 (9.60%, 95% CI: 7.20%–12.03%). Independent predictors in the GEE model included same contrast group (OR 2.52, 95% CI: 1.11–5.69, $P=0.027$), female sex (OR 2.03, 95% CI 1.06–3.88, $P=0.032$), younger age (OR 0.97 per year, 95% CI: 0.94–0.99, $P=0.019$), and first rechallenge exposure (OR 2.45, 95% CI: 1.33–4.52, $P=0.004$). Different-group switching with similar side chains was not independently associated with BTR.

Conclusion: BTR occurred in 9.60% of premedicated re-exposures. An alternative agent from the same contrast group was the most important modifiable predictor, while side-chain similarity alone did not significantly increase risk. This supports prioritizing contrast group switching when choosing an alternative agent.

Keywords: Allergic-like reaction, breakthrough reaction, contrast switching, iodinated contrast media, side-chain classification.

Intravenous iodinated contrast media (ICM) are widely used in computed tomography (CT) and other radiological investigations to improve tissue differentiation and lesion characterization. The volume of contrast-enhanced CT examinations has grown steadily. At Bangkok Metropolitan Administration General Hospital, the number of contrast-enhanced CT studies has increased from 4,418 studies in 2023 to 5,671 studies in 2025.

Allergic-like reactions to ICM are a recognized complication. Shifting from high-osmolar ionic CM to

modern nonionic low-osmolar agents has markedly reduced overall reaction rates, from 5.0%–15.0% with ionic agents to approximately 0.2%–0.7% with nonionic ones;⁽¹⁻³⁾ severe reactions occur in ~0.04% of administrations.⁽⁴⁾ Nevertheless, given the high volume of contrast use, even rare severe reactions represent an important patient safety concern.

A prior allergic-like reaction to CM is the strongest predictor of a subsequent reaction. Even with premedication, breakthrough reactions occur in ~10.0% of patients with a history of prior reaction.⁽⁵⁾ Current guidelines emphasize the selection of an alternative contrast agent (CA) in patients with prior reactions; the American College of Radiology (ACR) allows selected use of premedication, whereas the European Society of Urogenital Radiology (ESUR) does not recommend routine premedication. Nonetheless, allergic-like reactions may still occur—a phenomenon called a breakthrough reaction (BTR).

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Reported BTR rates vary across studies, from ~2.1% in one premedicated inpatient cohort to 6.0%–14.0% in other recent low-osmolar contrast cohorts.⁽⁶⁻⁸⁾

Recent evidence has suggested that selecting a CA from a different chemical group particularly one with a different N-(2,3-dihydroxypropyl) carbamoyl side-chain structure may reduce BTR risk beyond simple brand switching.^(9, 10) Vega F, *et al.* proposed classifying nonionic iodinated CAs into four groups (A–D) based on their side-chain structures and suggested a framework for selecting alternative CAs.⁽¹¹⁾ A 2025 joint consensus statement from the ACR and the American Academy of Allergy, Asthma and Immunology (AAAAI) subsequently de-emphasized routine premedication for mild prior reactions and placed greater weight on contrast group switching.^(12, 13)

Despite growing evidence, Thai data on iodinated contrast hypersensitivity are limited,⁽¹⁴⁾ and no Thai study has specifically reported the incidence and predictors of BTR in a premedicated rechallenge cohort. This study aimed to investigate the incidence of BTR at a single Thai tertiary hospital over a decade. Specifically, it aimed to identify independent predictors of BTR with a particular focus on the impact of same-group versus different-group switching and side-chain similarity on reaction risk.

Materials and methods

Study design and setting

This was a single-center retrospective cohort study conducted at the Radiology Section, Bangkok Metropolitan Administration General Hospital, Bangkok, Thailand. It was approved by the Bangkok Metropolitan Administration Human Research Ethics Committee (approval no.: S034hc/68_EXP). The requirement for informed consent was waived given the retrospective nature of the study and the use of de-identified data.

Study population

Of 25,540 patients who received CM in our institution between September 2015 and December 2025, we identified all patients who underwent a contrast administration timeout due to a prior allergic-like reaction. Patients were included if they were ≥ 15 years, had a documented prior allergic-like reaction to iodinated CM (at this or another institution), received a complete premedication regimen before

CM administration, and had complete documentation of the CA used, premedication received, and clinical outcome. Patients were excluded if their prior reaction was severe, as this precluded rechallenge under our institutional protocol. Of the 625 patients screened, 53 were excluded for the following reasons: ionic CM as index reaction ($n = 26$), no premedication received ($n = 16$), unknown index CA ($n = 6$), unknown index reaction symptoms or severity ($n = 2$), incomplete premedication (< 3 doses of oral prednisolone; $n = 2$), and nonintravenous contrast study (voiding cystourethrography; $n = 1$). The final study population comprised 572 contrast administrations from 210 patients (**Figure 1**).

Each patient could contribute multiple exposures if they underwent > 1 contrast administration during the study period. To account for the resulting within-patient correlation, all multivariate analyses used generalized estimating equations (GEE; see Statistical analysis).

Prevention protocol

All patients received our institutional standard oral premedication regimen, primarily based on ACR recommendations for premedication in use during the study period. The standard regimen was 50 mg oral prednisolone in 13 h, 7 h, and 1 h before contrast injection (three doses). Every administration of the 572 included a complete oral prednisolone regimen. In addition, eight (1.4%) received supplemental intravenous corticosteroids (hydrocortisone or dexamethasone) at the radiologist's discretion due to concerns about individual patient risk; in no case was intravenous corticosteroid administered as a replacement for the oral prednisolone regimen.

In addition, the CA was switched to any available agent different from the previously implicated brand and to which the patient had no prior history of reaction; agent selection was based on stock availability, without a structured switching algorithm.

Both the prior reaction record and the CA administered were documented in a dedicated timeout form completed by the radiology nurse before each injection, under the radiologist's supervision.

Contrast agent classification

All non-ionic iodinated CAs used at our institution were classified into four groups (A–D) according to the side-chain classification proposed by Vega F, *et al.*⁽¹¹⁾. Group A agents carry the N-(2,3-dihydroxypropyl)

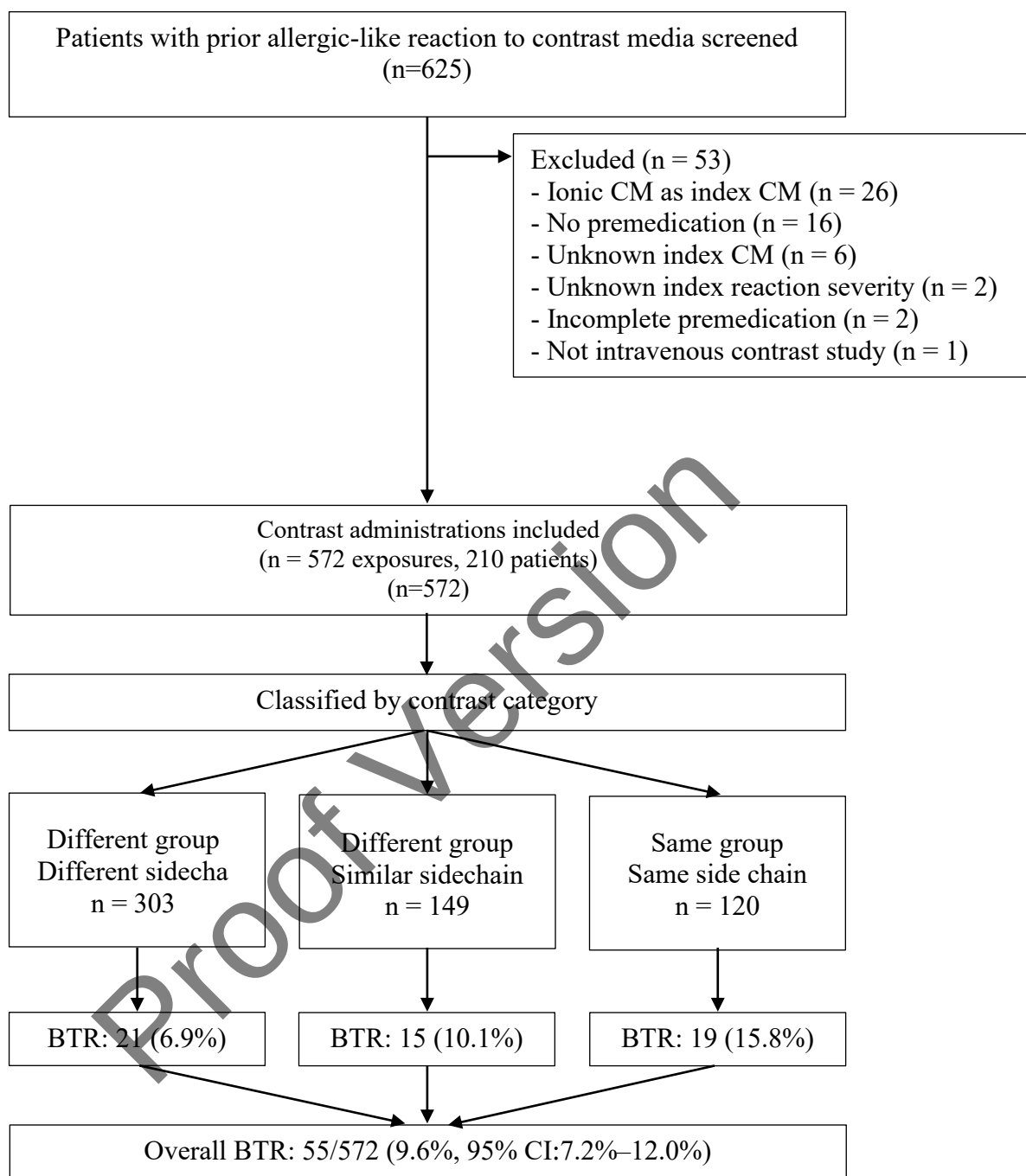


Figure 1. Patient flow diagram. CM, breakthrough allergic-like reaction; confidence interval; contrast media; BTR, ; CI.

carbamoyl side chain and include iohexol, iomeprol, ioversol, and iodixanol. Group B agents carry the N-(2,3-dihydroxypropyl)-N-methyl-carbamoyl side chain and include iobitridol. Group C agents carry both side chains and include iopromide. Group D agents carry neither side chain but include iopamidol. Only one Group C agent (iopromide) was stocked at our institution during the study period.

For each administration, the CA implicated in a prior reaction was considered as index CA. The relationship between the CA administered and the index CA was categorized as follows: (1) different group, different side chain (reference category); (2) different group, similar side chain (Groups A and C, or Groups B and C); or (3) same group, same side chain as the index CA.

Outcome definitions

The main goal was to identify BTR, an allergic-like reaction that happens after contrast is given to a premedicated patient and has a different CA than the one used for the initial procedure. Only allergic-like reactions were recorded; physiological reactions (such as nausea, warmth, or flushing without allergic features) were excluded. Reaction severity was classified as mild, moderate, or severe using the three-tier system for allergic-like contrast reactions described in the 2025 ACR/AAAAI consensus statement.⁽¹²⁾ Mild reactions were self-limited and confined to isolated cutaneous or upper airway findings, such as localized urticaria or pruritus, nasal congestion, sneezing, conjunctivitis, or rhinorrhea. Moderate reactions were more extensive but hemodynamically stable, including generalized urticaria or pruritus, diffuse erythema with normal vital signs, facial edema without dyspnea, throat tightness or hoarseness without stridor, and wheezing with minimal or no hypoxia. Severe reactions involved respiratory or hemodynamic compromise: diffuse erythema with hypotension, facial or laryngeal edema with stridor or hypoxia, bronchospasm with significant hypoxia, or anaphylactic shock. Severity relative to the index reaction and changes compared to the index reaction were recorded as decreased, unchanged, or increased.

Statistical analysis

The primary outcome (BTR incidence) was expressed as a proportion with a 95% confidence interval (CI) calculated using the normal approximation. Continuous variables are reported as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR) as appropriate. Categorical variables are reported as numbers and percentages.

For unadjusted comparisons, the Mann–Whitney U test was used to compare the age between the BTR and no-BTR groups, and Fisher's exact test was used for categorical variables. A Cochran–Armitage trend test was used to assess the dose-response relationship across contrast categories and sequential exposure numbers.

Since individual patients contributed a median of two exposures (IQR 1–3, maximum 22), standard logistic regression was not appropriate. Thus, we used GEE with an exchangeable correlation structure and robust sandwich standard errors to account for multiple exposures contributed by the same patient, providing population-averaged estimates of each predictor's effect. The model included the following covariates: contrast category (three-level categorical

variable with different groups/ side chains as reference), sex, age (continuous, centered at the mean), coexisting drug allergy, history of allergy to ≥ 2 contrast groups, and first re-challenge exposure versus subsequent exposures. Results are presented as odds ratios (OR) with 95% CI and statistical significance defined as $P < 0.05$. All analyses were performed using Stata (version 15; StataCorp, College Station, TX, USA). The GEE model was fitted using the xtgee command with family (binomial), link (logit), exchangeable correlation structure, and vce (robust) for robust sandwich standard errors.

Results

Study population

Between September 2015 and December 2025, 572 contrast administrations in 210 patients met the inclusion criteria. The number of exposures per patient ranged from 1 to 22, with a median of 2.0 (IQR 1.0–3.0). Of the 210 patients, 130 (61.9%) were women. Mean age was 58.5 ± 12.7 years (median 60.0 years, IQR 50.0–69.0). Sixty-four patients (30.5%) had a co-existing drug allergy. The index reaction was mild in 552 administrations (96.5%) and moderate in 20 (3.5%); no administration had a severe index reaction (this was an exclusion criterion). All 572 administrations received the standard oral prednisolone regimen (50 mg at 13, 7, and 1 h before injection). Eight administrations (1.4%) received additional intravenous corticosteroids at the radiologist's discretion, and none were administered as a replacement for oral prednisolone. Patient characteristics stratified by BTR status are presented in **Table 1**.

Regarding the CA administered, 372 administrations (65.0%) used Group A agent, 131 (22.9%) Group B agent, 29 (5.1%) Group C agent, and 40 (7.0%) Group D agent. By contrast, 303 administrations (53.0%) were classified as different group/different side chain (reference), 149 (26.0%) as different group/similar side chain, and 120 (21.0%) as same group/same side chain as the prior reaction.

Primary outcome: incidence of BTR

BTR occurred in 55 of 572 administrations to an overall incidence of 9.60% (95% CI 7.20%–12.03%). This is consistent with the 6.0–14.0% range reported in international studies.^(7, 8) **Table 2** shows BTR incidence by contrast category. The BTR rate was 6.9% (21/303) in the different group/different side-chain category (reference category), 10.1% (15/149) in the different group/similar side-chain category, and

Table 1. Characteristics of contrast media administrations with premedication in patients with prior allergic-like reactions (n = 572 exposures, 210 patients).

Characteristic	All exposures (n = 572)	BTR (n = 55)	No BTR (n = 517)	P-value
Age (years), mean $\pm$ SD	60.7 $\pm$ 12.1	56.8 $\pm$ 12.3	61.1 $\pm$ 12.0	0.015
Median (IQR)	62.0 (53.0–71.0)	59.0 (48.0–68.0)	62.0 (54.0–71.0)	
Female sex, n (%)	340 (59.4)	41 (74.5)	299 (57.8)	0.020
Index reaction severity, n (%)				
Mild	552 (96.5)	53 (96.4)	499 (96.5)	1.000
Moderate	20 (3.5)	2 (3.6)	18 (3.5)	
Co-existing drug allergy, n (%)	154 (26.9)	19 (34.5)	135 (26.1)	0.201
History of allergy to ≥ 2 contrast groups, n (%)	50 (8.7)	9 (16.4)	41 (7.9)	0.044

P-values by Mann-Whitney U test for age; Fisher's exact test for categorical variables.

BTR, breakthrough allergic-like reaction; IQR, interquartile range; SD, standard deviation.

Table 2. Incidence of breakthrough allergic-like reactions by contrast group category

Contrast group category	n	BTR n (%)	Unadjusted OR (95% CI)	P-value	Adjusted OR† (95% CI)
Different group, different side chain (reference)	303	21 (6.9)	1.00 (reference)	—	1.00 (reference)
Different group, similar side chain	149	15 (10.1)	1.50 (0.75–3.01)	0.269	1.40 (0.69–2.82)
Same group, same side chain	120	19 (15.8)	2.53 (1.30–4.89)	0.009	2.52 (1.11–5.69)*

P for trend = 0.006 (Cochran-Armitage trend test across contrast categories, from least to most similar to index reaction).

BTR, breakthrough allergic-like reaction; CI, confidence interval; OR, odds ratio.

Unadjusted OR by Fisher's exact test. †Adjusted OR from GEE model with exchangeable correlation, adjusted for sex, age, co-existing drug allergy, and history of allergy to ≥ 2 contrast groups.

* P = 0.027.

Table 3. Multivariate analysis of predictors of breakthrough allergic-like reactions: generalized estimating equations (GEE) model

Variable	aOR	95% CI	P value	
Contrast group category (reference: different group, different side chain)				
Different group, similar side chain	1.40	0.69–2.82	0.351	
Same group, same side chain	2.52	1.11–5.69	0.027	*
Female sex	2.03	1.06–3.88	0.032	*
Age (per 1 year increase)	0.97	0.94–0.99	0.019	*
Co-existing drug allergy	1.13	0.56–2.29	0.736	
History of allergy to ≥ 2 contrast groups	1.90	0.52–6.99	0.332	
First re-challenge exposure (vs. subsequent)	2.45	1.33–4.52	0.004	*

aOR, adjusted odds ratio; CI, confidence interval; GEE, generalized estimating equations.

GEE model fitted using Stata xtgee command with exchangeable correlation structure and robust sandwich standard errors. Unadjusted OR for first re-challenge vs. subsequent exposures: 2.44 (95% CI: 1.39–4.28), P = 0.002.

* Statistically significant at P < 0.05.

15.8% (19/120) in the same-group category. A significant increasing trend in BTR rate was observed across the three contrast categories, from least to most similar to the index CA (Cochran-Armitage trend test, P = 0.006).

BTR severity and clinical course

Of the 55 BTR events, 52 (94.5%) were mild and 3 (5.5%) moderate; no severe BTR occurred (**Table 3**). Compared with the index reaction, severity remained unchanged in 52 cases (94.5%), decreased in 1 case (1.8%), and increased in 2 (3.6%).

BTR predictors

On unadjusted analysis, administering a CA from the same group as the one causing the prior reaction was significantly associated with BTR (OR 2.53, 95% CI: 1.30–4.89, $P = 0.009$). Switching to a different group with a similar side chain was not significantly associated with BTR compared with the reference category (OR 1.50, 95% CI: 0.75–3.01, $P = 0.269$). First rechallenge exposures had a significantly higher BTR rate than subsequent ones (14.8% vs. 6.6%; unadjusted OR 2.44, 95% CI: 1.39–4.28, $P = 0.002$). When modelled categorically, BTR rates declined progressively with each subsequent exposure: 2nd exposure OR, 0.54 (95% CI: 0.26–1.12, $P = 0.097$), 3rd OR, 0.37 (95% CI: 0.14–0.97, $P = 0.044$), 4th OR, 0.34 (95% CI: 0.10–1.13, $P = 0.078$), and $\geq 5^{\text{th}}$ OR 0.15 (95% CI: 0.04–0.59, $P = 0.007$), all relative to the 1st exposure.

In the GEE multivariate model, four variables were independently associated with BTR (**Table 3**). Administering the same contrast group remained a significant predictor (adjusted OR 2.52, 95% CI 1.11–5.69, $P = 0.027$). Switching to a different group with a similar side chain was not significant (adjusted OR 1.40, 95% CI: 0.69–2.82, $P = 0.351$). Female sex (adjusted OR 2.03, 95% CI: 1.06–3.88, $P = 0.032$), younger age (adjusted OR 0.97 per year, 95% CI: 0.94–0.99, $P = 0.019$) and first re-challenge exposure (adjusted OR 2.45, 95% CI: 1.33–4.52, $P = 0.004$) were also independently associated with BTR. Co-existing drug allergy and history of allergy to ≥ 2 contrast groups were not significant in the adjusted model.

Discussion

In this 10-year retrospective cohort from a Thai tertiary hospital, the incidence of BTR to ICM despite premedication and contrast switching was 9.6%. This is consistent with published data (6.0%–14.0%),^(7,8) and confirms that BTR remains a clinically meaningful problem even when applying standard preventive measures.

The most important, clinically actionable finding of this study is that switching within the same contrast group, despite using a different brand or formulation, was associated with ~2.5-fold higher BTR risk than switching to a different contrast group. In contrast, switching to a different group with a similar side-chain structure did not significantly increase risk. This suggests contrast group membership is a more significant factor in BTR risk than side-chain similarity itself. Therefore, radiologists and departments should

prioritize switching to a different contrast group rather than simply choosing any nominally different agent.

These results are consistent with two independent meta-analyses showing that CM switching reduces recurrent hypersensitivity risk by 61.0%–69.0%.^(9,15) Kim PH, *et al.* similarly reported that switching to a CA with a different N-(2,3-dihydroxypropyl) carbamoyl side chain reduced both BTR risk and severity in a large Korean cohort.⁽¹⁰⁾ Our study extends this evidence to a Thai population and suggests that the group-level distinction is more important than side-chain similarity as the significant effect observed in binary analysis was entirely driven by the same-group subgroup.

Further evidence comes from a Thai institutional cohort. Pinyopornpanich K, *et al.* reported recurrent hypersensitivity reactions in 3 of 6 patients re-exposed to both iohexol and iodixanol (both Group A), whereas no recurrent reactions were observed in 12 patients exposed to both iodixanol (Group A) and iopamidol (Group D).⁽¹⁴⁾ While that study was not restricted to premedicated patients and did not use BTR as main outcome, the observed pattern aligns with the group-level effect in the current study.

We also observed a strong association between first rechallenge exposure and BTR risk. Patients undergoing their first rechallenge had a BTR rate of 14.8%, compared with 6.6% for subsequent exposures, with rates progressively declining with each additional exposure. This likely reflects the depletion of susceptible patients. Those experiencing a BTR at the first re-challenge are less likely to undergo further contrast studies. This results in a progressively lower-risk population at subsequent exposures. However clinical selection of lower-risk patients for repeated re-challenges may also play a role. Clinically, this suggests that the first rechallenge represents the highest-risk administration and warrants particularly careful monitoring and preparation.

Notably, no severe BTR occurred; BTR severity was the same or lower than the index reaction in 96.4% of cases. This is consistent with Kim PH, *et al.*, who reported that contrast switching was associated with reduced reaction severity in most patients,⁽¹⁰⁾ and with McDonal JS, *et al.* found that only 7.0% of repeat reactions were more severe than the index reaction, with just one severe reaction across 4,360 examinations.⁽¹⁶⁾ These findings suggest that using preventive measures, recurrent reactions are usually similar in severity to or even less severe than the initial reaction. However, due to the small sample size of BTR events in this study, these observations should be interpreted cautiously.

Female sex and younger age were also independent predictors of BTR in our study. Female predominance in contrast hypersensitivity has been previously reported and may reflect sex-related immunologic differences.⁽¹⁷⁾ The inverse association with age is less well understood and should be interpreted cautiously; it may reflect age-related differences in immune responsiveness or depletion of susceptibles among older patients who have undergone more previous contrast exposures.

History of allergy to ≥ 2 contrast groups was more frequent in the BTR group on unadjusted analysis, but this association was not retained in the multivariable GEE model. This likely reflects limited precision due to the small subgroup size (50 exposures, with nine BTR events), as well as attenuation after adjusting for other covariates and within-patient clustering.

Throughout the study period, our protocol for premedication was highly consistent. Ninety-eight point six per cent of administrations involved standard oral prednisolone, which made it impossible to compare different premedication regimens. Although this limits inference about premedication strategies, it reflects real-world practice and indicates that our BTR estimate is representative of this regimen. Recent evidence suggests that contrast substitution is more effective than steroid premedication alone in reducing recurrent reactions. McDonal, *et al.* reported a repeat reaction rate of 19.0% with the same ICM plus steroid premedication, compared with only 3.0% when a different ICM was used without premedication.⁽¹⁶⁾ Consistent with this result, recent guidelines, including the 2025 ACR/AAAAI consensus statement,^(12, 13) the 2025 updated ESUR guidelines,⁽¹⁸⁾ and the 2025 Canadian Association of Radiologists/Canadian Society of Allergy and Clinical Immunology (CAR/CSACI) practice guidance, increasingly emphasize contrast substitution and de-emphasize routine corticosteroid premedication.⁽¹⁹⁾ Our data emphasize the importance of contrast group switching as a primary preventive strategy. However, we cannot comment on the benefit of omitting premedication as this was not studied.

This study has several limitations. First, as a single-center retrospective study, its findings may not be generalizable to institutions with different patient populations, contrast formularies, or preventive practices. Second, although GEE was used to account for within-patient clustering, the retrospective design leaves the possibility of residual confounding by unmeasured factors, such as atopic history or other clinical susceptibility factors. Third, the moderate index reaction group was small ($n = 20$, with only 2 BTR

events), precluding meaningful analysis of the effect of index severity on BTR risk. Similarly, since no severe BTR occurred the study could not reliably assess predictors of severe recurrent reactions. Furthermore CA classification by side-chain group adheres to the framework proposed by Vega F, *et al.*⁽¹¹⁾ While this is the most structured approach currently available it is still a practical guide rather than a universally accepted standard. Consequently, comparisons with studies using different classification systems are limited. Furthermore, our institution's alternative contrast selection was based on local availability rather than a protocolized substitution algorithm, which might have introduced practice-based variability. Finally, the study spanned multiple annual procurement cycles so the specific CAs available at our institution likely changed over time although the preventive protocol remained largely consistent.

Conclusion

BTR occurred in 9.6% of contrast administrations within this Thai cohort, mirroring international experience. Exposure to a CA from the same group as the index reaction was the most important modifiable predictor of BTR, whereas side-chain similarity alone did not significantly increase risk when selecting a different group. These findings support prioritizing contrast group switching over simple side-chain matching when selecting an alternative agent for patients with prior reactions and consistent with recent international guidance, including the 2025 ACR/AAAAI consensus statement, the 2025 updated ESUR guidelines, and the 2025 CAR/CSACI practice guidance. The initial re-challenge posed the greatest risk and therefore requires particularly careful clinical preparation. Future multicenter studies in Thailand are essential to validate these findings.

Author contributions

BT contributed substantially to the concept and design of this study, acquiring the data, reviewing the literature and its analysis and interpretation, acquiring the data, drafting the manuscript, and edited the manuscript critically for important intellectual content. The author approved the final version submitted for publication and take responsibility for statements made in the published article.

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Conflict of interest statement

All authors have completed and submitted the International Committee of Medical Journal Editors Uniform Disclosure Form for Potential Conflicts of Interest. All authors declare that they have no conflicts of interest.

Data sharing statement

All data generated or analyzed in the present study are included in the published article. Further details are available for non-commercial purposes from the corresponding author upon reasonable request.

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