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# Is gender still a predisposing factor in contrast-media associated adverse drug reactions? A systematic review and meta-analysis of randomized trials and observational studies

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ABSTRACT

*Objective:* To evaluate the role of gender as a risk factor for developing contrast media-associated adverse drug reactions (CM-ADRs) by comparing the incidence of CM-ADR between male and female patients according to study design, ADR type, and computed tomography (CT) examination.
*Material and methods:* We systematically searched three electronic databases for eligible studies. In the studies included (n = 18), we assessed effect estimates of the relative incidence of CM-ADR, analysed by experimental design, ADR type and CT examination. This was calculated by using a random effects model if clinical conditions showed heterogeneity; otherwise, a fixed effects model was used.
*Results:* We identified 10,776 patients administered CM. According to the designs, studies were classified into randomised controlled trials (RCTs) and observational studies. Results were as follows: risk ratio (RR) = 1.07 (95% confidence interval (CI): 0.79–1.46, P = 0.66) for RCTs, and RR = 0.77 (95% CI: 0.58–1.04, P = 0.09) for observational studies. The results of analysis according to ADR type and for undergoing CT demonstrated that the incidence of CM-ADR did not differ between males and females.
*Conclusions:* We found no significant difference in the incidence of CM-ADRs between male and female patients according to study design, ADR type, or CT examination. Future studies to determine why gender has shown different roles as a risk factor between CM-ADRs and non-CM ADRs are needed.


## 1. Introduction

The World Health Organization (WHO) defines an adverse drug reaction (ADR) as a noxious, unintended, and unavoidable response to medication [1]. Several clinical research and pharmacovigilance (PV) studies have been conducted to determine the types of ADRs and the risk factors associated with them [2–4]. Such studies have been conducted to study ADRs not only for medications but also for contrast media (CM) used in radiologic imaging [5–8].

In clinical practice, the management of patients requires an investigation of predisposing risk factors responsible for the development of ADRs [9]; one of the most common risk factors is gender [3,10]. It is known that male and female patients respond differently to medications because of pharmacokinetic, pharmacodynamic, and hormonal differences between them. Generally, women are known to develop ADRs more frequently than men do [4,11].

After investigating previous reports of qualitative studies, some review articles concluded that female gender was a risk factor for developing CM-ADRs [9,10,12]. However, these reviews did not seem to identify gender definitively as a risk factor for developing CM-ADRs and covered only a limited number of studies [9,10,12]. Additionally, PV studies based on spontaneous ADR reports yielded conflicting results with respect to the role of gender as a risk factor for developing ADR. For example, a spontaneous report about CM-ADRs showed that male subjects developed 55% more ADRs than females [13], while another PV study based on spontaneous reports

*Abbreviations:* ADR, Adverse drug reaction; CIN, Contrast induced nephrotoxicity; CM, Contrast media; CM-ADR, Contrast media associated ADR; CT, Computed tomography; MOOSE, Meta-analysis Of Observational Studies in Epidemiology; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PV, Pharmacovigilance.

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sent to the US Food and Drug Administration demonstrated that ADRs were three times more common in women than in men [14]. Furthermore, a recent PV study demonstrated that CM-induced ADRs and non-CM-induced ADRs responded differently to gender differences, but the incidence of CM-ADR showed no difference between the genders [2]. These discrepancies among outcomes of spontaneous CM-ADR reports were probably caused by the absence of a control group; thus, the previous meta-analyses seem to provide the most definitive result that female gender is not a risk factor for developing CM-ADRs. However, these meta-analyses had limited statistical power [15,16], indicating the need for systematic research involving larger sample sizes to assess gender as a risk factor in developing CM-ADRs.

Similarly, studies investigating the effect of gender in the development of renal and non-renal CM-ADRs yielded conflicting outcomes [17,18]. A large trial was conducted to differentiate between CM-independent acute kidney injury and CM-associated renal toxicity, also known as CM-induced nephrotoxicity (CIN). This study investigated the effects of various risk factors in developing CIN, but did not consider gender as a risk factor [19]. The effects of gender on non-renal CM-ADRs were investigated in several studies, also yielding conflicting results [7,10,15]. Additionally, the effects of gender on the incidence of CM-ADRs related to CT examination varied markedly among the different studies [16,20,21].

Unlike non-CM-induced ADRs, qualitative and quantitative evidence to support gender as a risk factor for developing CM-ADRs remains controversial. The lack of evidence has restricted further investigations of the poorly defined pathogenesis and more prospective trials focusing on the gender factor in CM-ADR development. Thus, in the present study, the role of gender as a predisposing factor for CM-ADR development was investigated through systematic reviews and meta-analysis. Additionally, the effects of gender on both types of CM-ADR, CIN and non-renal CM-ADR, were evaluated, and the incidence of CM-ADR after CT was examined.

## 2. Material and methods

We conducted a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statements [22,23].

### 2.1. Data sources and study selection

We searched Medline, the Cochrane library, and Embase for eligible studies that reported adverse drug reactions to contrast media according to gender. The following keywords were searched: “contrast media,” “contrast agent,” “adverse drug reaction,” “adverse drug event,” “contrast-induced adverse drug reaction,” “contrast-induced adverse drug event,” “gender difference,” “sex difference,” “gender,” “sex,” “trial,” “intervention,” “human,” “randomized,” “non-randomized,” and “observational”. RCTs and observational studies that were published were included in the present meta-analysis if the outcomes reported the number of males and females who showed adverse drug reactions after administration of contrast media. There was no age limitation in eligible studies. The review was restricted to original articles that were reported in English. We included only full-text articles that contained sufficient information to assess; which provided the number of patients showing adverse reactions after administration of contrast media. Two reviewers (HY and YJ) independently selected studies according to eligibility criteria. Disagreements in study selection were solved by a third reviewer (EY) or by discussion.

### 2.2. Data extraction and quality assessment

The information in all identified articles was reviewed and extracted independently by two reviewers (HY and SY). The first author, year of publication, total number of participants, contrast agent type, study design, types of examination, and adverse drug reactions were extracted.

A quality assessment was independently conducted by two reviewers using Cochrane’s “Risk of Bias” assessment tool for randomized clinical trials [24], and, according to recommendations for assessing literature quality assessments [24,25] we proceeded with quality assessment for observational studies using the Newcastle-Ottawa Scale (NOS), which gives a maximum score of nine; in which a score of five or more indicates medium to high study quality [26]. These bias assessment tools were designed to assess the risk of bias in each study included in the present meta-analysis. These tools include a judgment and a support for the decision for each entry in a table, where each entry reports a specific feature of each included study [24–26]

### 2.3. Data synthesis and analysis

The primary outcome of the present analysis was to compare the incidence of contrast-induced adverse drug reactions between men and women, which was analyzed according to study designs such as randomized and observational studies. The subgroup analysis was performed according to two types of CM-ADRs. The first was renal CM-ADRs, called CIN, and the next was non-renal CM-ADRs. This accreditation of the types of contrast-induced adverse drug reactions was conducted according to the guidelines and literature [27,28]. We also conducted an analysis to investigate the differences in the incidence of contrast-induced adverse drug reactions based on gender according to the method of examination, which was CT. To calculate the incidence of ADRs, we counted the number of patients showing CM-ADRs instead of the number of ADRs developed, which was aimed to prevent overestimation caused by analyzing the number of ADRs that developed in the total number of patients [20]. For all studies, we referred to the effect estimates of relative incidence from RCTs and observational studies. The relative incidence of contrast-induced adverse drug reactions was calculated by pooling effect sizes with a 95% confidence interval (CI) using a random effects model if clinical conditions showed heterogeneity, otherwise, a fixed effects model was used. The Higgins’ $I^2$ statistic and the chi-square-based Q-test were used to assess heterogeneity among studies, which was denoted as $P < 0.10$, $I^2 > 40\%$, or both. Publication bias was evaluated with funnel plots and Egger’s test. Statistically significant association was determined as $P < 0.05$. Data from eligible studies were analyzed using Review Manager 5 software (version 5.3.5, The Nordic Cochrane Centre, The Cochrane Collaboration) and Comprehensive Meta-analysis software (version 2, Englewood, NJ 07631 USA).

## 3. Results

### 3.1. Study selection

In total, 6844 articles were identified after the literature search. After evaluating duplicates, non-clinical trials, non-full text articles, and studies using other languages except for English, 654 studies were found to be potentially relevant. Studies that did not report adverse drug reactions of CM according to the differences in male and female were excluded, and a manual search of the reference list of each article found one study. Finally, 18 studies were included in the analysis (Fig. 1).