

**Incidence and risk factors of low-osmolar iodinated contrast media related immediate hypersensitivity reactions: A longitudinal study based on a real-time monitoring system**

Running title: Risks of contrast media hypersensitivity

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**Conflict of interest statement**

The authors declare that there is no conflict of interest regarding the publication of this article.

## Abstract

**Objectives:** We investigated the incidence of immediate hypersensitivity reaction (HSR) focusing on the types of low osmolar contrast media (LOCM) and accumulated exposures to LOCM.

**Methods:** This cohort study included all consecutive patients who underwent LOCM-enhanced computed tomography scan from 2012 through 2014. Five LOCMs (iobitridol, iohexol, iomeprol, iopamidol, and iopromide) were used. All patients were monitored for adverse events and new symptoms and signs were recorded in the Contrast Safety Monitoring and Management System (CoSM<sup>2</sup>oS) in real-time.

**Results:** The overall incidence of immediate HSR to LOCM was 0.97% (2,004 events resulting from 205,726 exposures). Incidence was significantly different depending on the presence of a previous history of HSR to LOCM (0.80% in patients with no history and 16.99% in patients with a positive history of HSR to LOCM,  $P = .001$ ). The incidence of HSR to individual LOCMs ranged from 0.72% (iohexol) to 1.34% (iomeprol), but there were no significant differences across the five LOCMs. A longitudinal analysis demonstrated that the incidence of HSR gradually increased with increased previous exposure to LOCM (HR=2.006 (1.517-2.653),  $P < .001$ ). However, this accumulated increase in risk was observed in subjects who had experienced HSR to LOCM, but not in subjects who had never experienced LOCM-induced HSR before.

**Conclusion:** The incidence of HSR was not significantly different across the five LOCMs used in the study. Repeated exposure to LOCM did not increase the risk of HSR among subjects who never experienced HSR to LOCM.

**Key words:** Contrast Media, Hypersensitivity, Incidence, Risk Factors, Secondary Prevention.

## Resumen

**Objetivos:** Estudio de la incidencia de reacciones de hipersensibilidad inmediata frente a diferentes medios de contraste de baja osmolaridad, así como la incidencia global de dichas reacciones con estos contrastes yodados.

**Métodos:** Estudio de cohortes en el que se incluyó de forma consecutiva a todos los pacientes a los que se realizó TAC con contraste yodados de baja osmolaridad durante los años 2012 a 2014. Se emplearon 5 contrastes yodados: iobitridol, iohexol, iomeprol, iopamidol, and iopromide. En todos los pacientes se valoró la presencia de efectos adversos. La aparición de cualquier síntoma fue registrada en el mismo momento de su aparición en el Contrast Safety Monitoring and Management System (CoSM2oS) in real-time.

**Resultados:** La incidencia global de reacciones de hipersensibilidad inmediata a medios de contraste yodados de baja osmolaridad fue de 0.97% (2,004 reacciones en 205,726 exploraciones con contraste). La incidencia fue significativamente mayor en los pacientes con historia previa de reacción adversa (16,99%) frente a tan solo 0,80% en los pacientes sin historia previa de reacción ( $p = .001$ ). La incidencia de estas reacciones osciló desde el 0.72% con iohexol al 1.34% con iomeprol, sin alcanzar diferencias significativas entre los cinco contrastes. Un análisis longitudinal mostró que la incidencia de reacciones inmediatas de hipersensibilidad se incrementa de forma gradual en los pacientes con historia de reacciones previas con medios de contraste yodados ( $CR=2.006$  (1.517-2.653),  $P < .001$ ). este incremento solo se observaba en los pacientes con historia de reacciones previas, pero no en los sujetos sin historia previa de estas reacciones.

**Conclusión:** La incidencia de las reacciones de hipersensibilidad inmediata no fue significativamente diferente entre ninguno de los 5 contrastes utilizados en el estudio. Exposiciones repetidas a estos medios de contraste no aumentan el riesgo de este tipo de reacciones de hipersensibilidad inmediata en los pacientes que no habían presentado previamente este tipo de reacciones.

**Palabras clave:** Medios de Contraste yodados, Hipersensibilidad, Incidencia, Factores de riesgo, Prevención secundaria.

## Introduction

Hypersensitivity reaction (HSR) to drugs is an important source of morbidity and mortality. Increased use of contrast agents has resulted in increased incidence of drug sensitivity reactions, and contrast agents have become a major cause of drug hypersensitivity [1]. Although most reactions are mild to moderate, severe immediate reactions induced by low osmolar contrast media (LOCM) occur with a frequency of 0.02-0.04%, with an estimated death rate of 1 in 100,000 examinations [2]. In many studies, the most significant risk factor for an immediate HSR was a previous immediate reaction [3-5]. The osmolality of contrast agent is another obvious risk factor for hypersensitivity. High osmolar contrast media (HOCM) have been replaced by LOCMs since the late 1980s and are no longer used worldwide [6]. The incidence of severe immediate reactions was reduced up to 10-fold in patients given an LOCM after previously experiencing a reaction to HOCM [7]. Prevention strategies for high risk patients, such as changing the type of agent administered or premedication regimens have been used, and their effectiveness on reducing the incidence of hypersensitivity have been reported [8-11].

However, there is no clear evidence for differences in risk of an immediate HSR within the same class or for the accumulated effects of repeated LOCM exposure. Allergic-like HSRs induced by HOCM were considered to be a phenomenon caused by non-specific direct histamine release [12]. The effect of repeated exposures has been overlooked because the mechanism of contrast media hypersensitivity was believed to be a non-IgE-mediated reaction [13, 14]. Recently, growing evidence has suggested that some reactions, especially more severe reactions, can be triggered by an IgE-dependent mechanism [14-17]. In IgE-mediated responses, repeated exposures could enhance the possibility of allergic sensitization through T-cell and IgE memory [18, 19] and increase HSR to the exposed allergen. In this

study, we investigated whether the risk of immediate LOCM hypersensitivity is increased by repeated exposures to LOCM as well as specific types of LOCMs.

## Methods

### Study subjects and monitoring of contrast media hypersensitivity

This study included all patients who underwent an LOCM-enhanced computed tomography (CT) examination from July 2012 through June 2014 in the Seoul National University Hospital.

After administration of LOCM, subjects were monitored for one hour to determine whether an immediate HSR occurred. Symptoms and signs potentially suggesting immediate reaction to LOCM were monitored in real-time by trained radiology nurses and were recorded in the electronic medical record (EMR)-based Contrast Safety Monitoring and Management System (CoSM<sup>2</sup>oS). Through this system, information such as types of agents, pretreatment, and response to re-exposure of contrast media in patients who have previously undergone LOCM hypersensitivity was recorded [10]. The system automatically recommends a premedication regimen in accordance with the severity of the previous response when an exam using contrast agents is ordered for a patient with a history of LOCM hypersensitivity [10, 20]. Other data such as comorbidities, presence of allergic diseases (including allergic asthma, rhinitis, and chronic urticaria), information regarding LOCM, previous history of exposure to LOCM, and any previous immediate HSR to contrast media were retrospectively collected from the EMR.

Throughout the study period, five kinds of LOCM were used for enhancement of CT scans: iobitridol (Xenetix<sup>®</sup>), iohexol (Omnipaque<sup>®</sup>, Omnihexol<sup>®</sup>, Bonorex<sup>®</sup>), iomeprol (Iomeron<sup>®</sup>),

iopamidol (Pamiray<sup>®</sup>, Scalux<sup>®</sup>), and iopamide (Neovist<sup>®</sup>, Ultravist<sup>®</sup>).

This study was approved by our institutional review board. The requirement for informed consent was waived and participant privacy was protected in a secure manner.

### **Severity of immediate HSR**

Immediate HSR was defined as a reaction that occurred within one hour of LOCM administration. Patient symptoms and signs were classified into three categories based on the American College of Radiology (ACR) manual on Contrast Media: mild, moderate, or severe [21]. Mild reactions included limited urticaria, pruritus, cutaneous edema, nasal congestion, rhinorrhea, and conjunctivitis. Moderate reactions included diffuse urticaria, erythema, facial edema without dyspnea, laryngeal edema, and mild wheezing without hypoxia. Severe reactions included signs and symptoms that are often life-threatening such as diffuse erythema, edema with dyspnea, hypotension (defined as systolic blood pressure < 90 mmHg), laryngeal edema with hypoxia, wheezing with hypoxia, unresponsiveness, cardiopulmonary arrest, and clinically manifested arrhythmias.

### **Statistical analysis**

The incidence of immediate reaction was calculated by dividing the number of cases who experienced an immediate HSR to LOCM by the number of total cases where contrast-enhanced CT was used during the study period. The incidence of LOCM hypersensitivity in patients with underlying diseases or previous exposure to LOCM were calculated by dividing the number of patients with LOCM hypersensitivity by the total number of patients with these conditions. The chi-square ( $\chi^2$ ) statistic was used to compare the incidence rate between groups. Risk factors for LOCM hypersensitivity were determined using univariate and

multivariate regression model. Analyses were adjusted for age, gender, presence of allergy, previous LOCM exposure numbers, and history of previous LOCM hypersensitivity. Univariate analysis was performed to investigate the relationships between underlying diseases and immediate HSR to LOCM. Regression method was used to test p value for trend of increased accumulated effect of previous exposures on LOCM hypersensitivity. A forward stepwise model was used, with the likelihood ratio criterion of a *P* value less than 0.05 to retain a variable; all analyses were performed using the software package Version 24.0 (SPSS, Inc., Chicago, IL).

## Results

### *Incidence of immediate hypersensitivity to LOCM*

Among 205,726 exposures to LOCM in 86,328 patients, 2,004 events of immediate HSRs occurred in the study period, with an overall incidence of 0.97% (Table 1). Incidence of mild, moderate, and severe reactions was 0.85%, 0.10%, and 0.02%, respectively. Among the 2,004 cases of immediate HSRs, 81.0% (1,623 of 2,004 events) were newly developed cases and the remaining 381 cases (19.0%) were recurrent cases in patients who already had a history of immediate HSR to LOCM. Previous history of hypersensitivity to LOCM significantly predisposed patients to future HSRs on  $\chi^2$  test ( $P = .001$ ). While the incidence rate for the first reaction among patients with no history of previous reactions was 0.80% (1,623 events of 203,483 exposures), the incidence among patients who had a history of hypersensitivity was 16.99% (381 events of 2,243 exposures).

The incidence of HSR to individual LOCMs ranged from 0.72% (iohexol) to 1.34% (iomeprol), but there were no significant differences across the five LOCMs (Table 2). Moderate to severe reactions were less frequent in patients given iopamidol compared with

other agents (8.5% vs. 13.6%,  $P = 0.045$  on  $\lambda^2$  test, Fig 1). Although the proportion of severe reactions was the highest in the iobitridol group at 4.5%, the results were not statistically significant. The proportion of that experienced hypersensitivity following a previous immediate LOCM HSR was different according to the type of LOCM ( $P < 0.001$  on  $\lambda^2$  test). It was highest in patients with hypersensitivity to iopromide (36.6%) and lowest in patients with iomeprol (11.1%) (data not shown).

### ***Risk factors of LOCM hypersensitivity***

Multivariate regression analysis showed that the most significant risk factor for development of LOCM hypersensitivity was a history of previous LOCM hypersensitivity (hazard ratio (HR) = 40.693, 95% CI 35.466-46.692,  $P < 0.001$ ). This was followed by age under 50 years (HR = 2.113, 95% CI 1.912-2.336,  $P < 0.001$ ), presence of allergies such as asthma, allergic rhinitis, or chronic urticaria (HR = 1.621, 95% CI 1.280-2.051,  $P < 0.001$ ) [asthma (HR = 1.476, 95% CI 1.082-2.013), allergic rhinitis (HR=1.502, 95% CI 1.041-2.166), chronic urticaria (HR=2.535, 95% CI 1.384-4.645)], female gender (HR = 1.291, 95% CI 1.117-1.417,  $P < 0.001$ ), and previous exposure to LOCM (HR=1.178, 95% CI 1.022-1.358,  $p < 0.001$ ).

Patients with comorbid allergic diseases (2.6%,  $P = 0.001$ ) such as asthma (2.4%,  $P = 0.015$ ), allergic rhinitis (2.4%,  $P = 0.036$ ), or chronic urticaria (4.0%,  $P = 0.006$ ) had a higher incidence of immediate LOCM hypersensitivity. Patients with cancer (2.1%,  $P = 0.001$ ) or chronic liver disease (3.1%,  $P = 0.001$ ) also showed higher incidence of LOCM hypersensitivity (Table 3). The proportion of patients who received premedication was not different between patients with or without these underlying diseases.

### ***Longitudinal analysis of the risk of HSR based on cumulative exposure to LOCM***

The number of previous exposures to LOCM affected the difference in the incidence of HSR to LOCM in overall. The incidence of immediate LOCM hypersensitivity gradually increased with the number of previous exposures ( $P$  for trend  $<0.001$ , Fig 2A). The accumulated effect of previous repeated exposures on incidence of LOCM hypersensitivity was dependent on the presence of an LOCM hypersensitivity history. Patients with a history of HSR to LOCM showed a sharp increase in repeated exposures and plateaued at 6 or more exposures (Fig 2B). In patients without a previous history of LOCM hypersensitivity, the incidence did not increase in response to repeated exposures (Fig 2C).

The number of previous exposures to LOCM was not higher in patients with allergic diseases. However, patients with cancer (3.7 times in patients with cancer,  $P = 0.016$  on  $\lambda^2$  test), or chronic liver disease (5.8 times in patients with chronic liver disease,  $P = 0.005$  on  $\lambda^2$  test) were more frequently exposed to LOCM than those without these diseases.

### **Discussion**

This study monitored 205,726 cases in which LOCM were administered for enhanced CT examination in a single institution over a two-year period. Incidence and risk factors of HSR to LOCM were evaluated. Complete enumeration of large numbers of CT cases was possible through our electronic medical record (EMR)-based Contrast Safety Monitoring and Management System (CoSM<sup>2</sup>oS).

The incidence of hypersensitivity to LOCM has been reported in many studies which ranged from 0.31 to 1.34 [22-26], and shows marked decline over time through use of interventions for high-risk patients. In this study, the overall incidence of LOCM hypersensitivity was

0.97%, which is similar to results from other studies [22, 23]. The incidence of hypersensitivity in patients with a history of previous reactions, which accounted for 1.1% of total patients, was about 20 times higher than the incidence in patients without a previous history.

Several methods have been used to prevent LOCM hypersensitivity [27-29]. As previous history of hypersensitivity to LOCM is a major risk factor for further LOCM hypersensitivity [30], and several preventive strategies have been used for at risk patients. Accurate documentation of the contrast agent that induced the response, and history of iodine allergy should be evaluated [31], because previous history of hypersensitivity is the greatest risk factor. Premedication before LOCM injection is widely used to lower the incidence of hypersensitivity in patients with previous hypersensitivity and some studies suggest that the stratified premedication method according to the severity of index reaction could be effective and safe as a prophylactic measure while minimizing the use of steroids [10, 20]. Along with premedication, changing the LOCM administered is also an important strategy to reduce the risk of recurrence [20]. Although changing the LOCM to another agent in the same class has historically been viewed to have little or no benefit, recent ACR guidelines stated that changing contrast media within the same class of LOCM may help reduce the risk of recurrent HSRs to LOCM [32].

In the present study, the incidence of HSRs was not significantly different across the five LOCMs used. There is still a controversy regarding differences in incidence of hypersensitivity between different LOCM [7, 33-38] since the results of previous studies were inconsistent. Although several studies have shown no difference in the incidence of adverse drug reactions resulting from administration of different agents [7, 36-38], others reported that the incidence of LOCM hypersensitivity was higher with use of specific agents

[33, 35]. In previous studies evaluating incidence of hypersensitivity to LOCMs, risk factors such as previous use of LOCM, previous history of hypersensitivity, or comorbidities were not considered.

Our study showed an increased risk of LOCM hypersensitivity with repeated exposures to LOCM. Incidence of LOCM hypersensitivity showed a linear increase with number of previous exposures to LOCM that resulted in HSRs. Few studies describing the cumulative effect of repeated exposures to LOCM on drug hypersensitivity have been undertaken. Repeated exposures to LOCM increased the risk of adverse reactions in patients with hepatocellular carcinoma [39], however, in a nested case-control study, the number of exposures to LOCM was lower in hypersensitivity cases than in control [4]. IgE-mediated sensitization may be a possible explanation for increased incidence of HSR with repeated exposure. Growing evidence demonstrates that IgE-mediated allergic reactions may be at least partly involved in immediate LOCM hypersensitivity [17, 40]. However, it is still unclear whether immediate HSR to LOCM is IgE-dependent or IgE-independent (such as direct mast cell activation or complement activation). In the current study, immunological mechanisms were not determined by allergy tests, so the mechanism involved in LOCM hypersensitivity remain unclear. As HSRs were more frequent and more severe with repeated exposure to the same LOCM compared to different LOCM [10, 20], the possibility of immunologic memory in cases of hypersensitivity to LOCM is substantial. Although there is a sharp increase in the incidence of hypersensitivity by number of previous exposures in patients with a history of HSRs, the incidence did not increase in patients without a history of hypersensitivity to LOCM. A previous study reported that patients who have had previous exposure to LOCM without a reaction have lower risk of hypersensitivity [23]. These results suggest that repeated exposure itself may be not a significant risk factor of LOCM

hypersensitivity if there was no a history of hypersensitivity to LOCM, but there is a possibility that IgE-mediated sensitization might increase the risk of hypersensitivity in certain susceptible patients. Further investigations to determine whether exposure to all kinds of LOCM could increase sensitization, and which patients are susceptible to the LOCM sensitization, are necessary.

Several other risk factors for LOCM hypersensitivity have been identified [23, 30, 41, 42]. In addition to past history of LOCM hypersensitivity, the presence of allergic disease, female gender, and younger age are associated with increased risk of HSRs. In the present study, chronic urticaria, which was not previously identified as a risk factor for LOCM hypersensitivity, was associated with increased incidence of LOCM hypersensitivity with a high hazard ratio value. However, LOCM HSRs in patients with chronic urticaria were exacerbations of preexisting urticaria, and none of these patients had systemic reactions. The correlation between patients' underlying diseases other than allergic diseases and LOCM hypersensitivity has not been studied extensively. Cardiac disease [43], renal insufficiency, and hyperthyroidism [44] are possible risk factors. However, a recent study reported low incidence of ADRs regardless of underlying diseases except for allergic diseases [23]. In the present study, incidence of LOCM hypersensitivity was higher in patients with cancer and chronic liver disease. Although there evidence is lacking for the association between these underlying diseases and LOCM hypersensitivity, it is possible that repeated exposure to LOCM in patients with cancer or chronic liver disease increased the risk of hypersensitivity because they were more frequently exposed to LOCM.

The main findings of the present study are that repeated exposure to LOCM can increase the risk of hypersensitivity and that there is still controversy regarding differences in the incidence of hypersensitivity among different types of LOCM. There are several limitations

in the present study. First, contrast agents were not selected by randomization. Rather, a single contrast agent was preselected for each organ-specific CT by the corresponding radiology subspecialty to be used for a certain period. The contrast agent was changed when the patients had a previous HSR to an LOCM. Therefore, LOCM selection was not random and varied depending on patient characteristics. Second, when a patient had experienced a HSR in another center in the past, the agent responsible was sometimes unknown, so some patients may have been re-exposed to the agent responsible for the adverse effect. A larger, prospective, controlled follow-up study to evaluate the mechanisms underlying LOCM hypersensitivity will be of great value to support safer use of LOCM.

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**Table and figure legends**

**Table 1. The incidence of immediate LOCM hypersensitivity**

	<b>First event (n=203,483)</b>	<b>Recurred event (n=2,243)</b>	<b>Total (n=205,726)</b>
<b>Mild reaction</b>	1,428 (0.70%)	320 (14.27%)	1,748 (0.85%)
<b>Moderate reaction</b>	164 (0.08%)	46 (2.05%)	210 (0.10%)
<b>Severe reaction</b>	31 (0.02%)	15 (0.67%)	46 (0.02%)
<b>Overall</b>	1,623 (0.80%)	381 (16.99%)	2,004 (0.97%)

LOCM, low osmolar contrast media

**Table 2. The incidence of immediate hypersensitivity to LOCMs according to individual agents**

Index term	ICM	Number of exposure	Incidence of HSR	Incidence of severe HSR
	Osmolarity, mOsm/kg			
<b>Iopamidol</b>	<b>300</b>	16,894	1.28%	0.01%
<b>Iobitridol</b>	<b>350</b>	27,363	0.88%	0.04%
<b>Iohexol</b>	<b>350</b>	78,586	0.72%	0.01%
<b>Iopromide</b>	<b>370</b>	67,590	1.00%	0.02%
<b>Iomeprol</b>	<b>400</b>	15,293	1.34%	0.04%

LOCM, low osmolar contrast media;

HSR, hypersensitivity reactions

ICM, iodinated contrast media;

**Table 3. The incidence of LOCM hypersensitivity reaction in specific comorbid conditions**

	Incidence of HSR, %		p value	Exp (B)	Lower end	Upper end	p value
	Patients with comorbidity	Patients without comorbidity					
<b>Allergic diseases</b>	2.6	1.6	0.001	1.621	1.280	2.051	0.001
<b>Asthma</b>	2.4	1.6	0.015	1.476	1.082	2.013	0.014
<b>Allergic rhinitis</b>	2.4	1.6	0.036	1.502	1.041	2.166	0.029
<b>Chronic urticaria</b>	4.0	1.6	0.006	2.535	1.384	4.645	0.003
<b>Diabetes</b>	1.8	1.6	0.091	1.149	0.979	1.349	0.088
<b>Hypertension</b>	1.4	1.7	0.073	0.746	0.706	1.012	0.067
<b>Angina</b>	1.3	1.7	0.093	0.803	0.624	1.034	0.089
<b>Dyslipidemia</b>	1.5	1.6	0.443	0.905	0.711	1.151	0.414
<b>Chronic kidney disease</b>	1.2	1.6	0.320	0.748	0.455	1.228	0.251
<b>Cancer</b>	2.1	1.1	0.001	1.914	1.713	2.139	0.001
<b>Chronic liver disease</b>	3.1	1.5	0.001	2.064	1.769	2.408	0.001

HSR, hypersensitivity reactions;

LOCM, low osmolar contrast media;

\*The incidence of LOCM hypersensitivity according to underlying diseases was calculated by dividing the number of all patients by the number of patients with ICM hypersensitivity.

Figure 1. The proportion of severity profile according to individual agents.

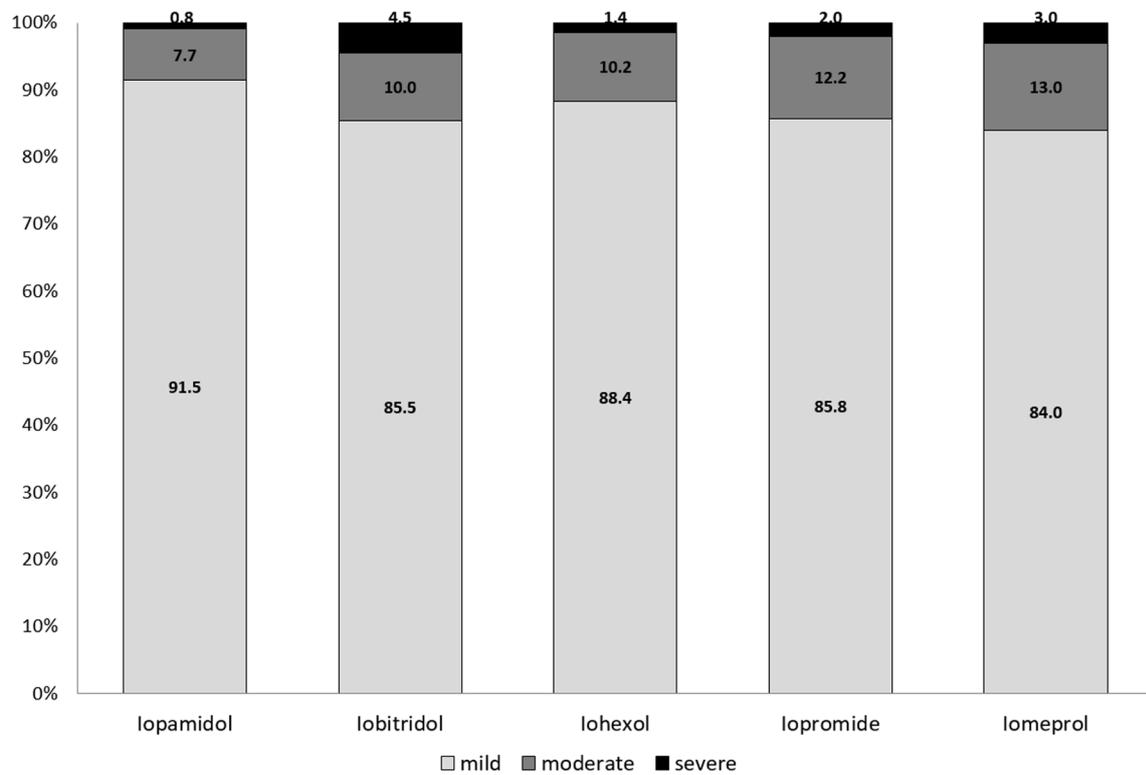
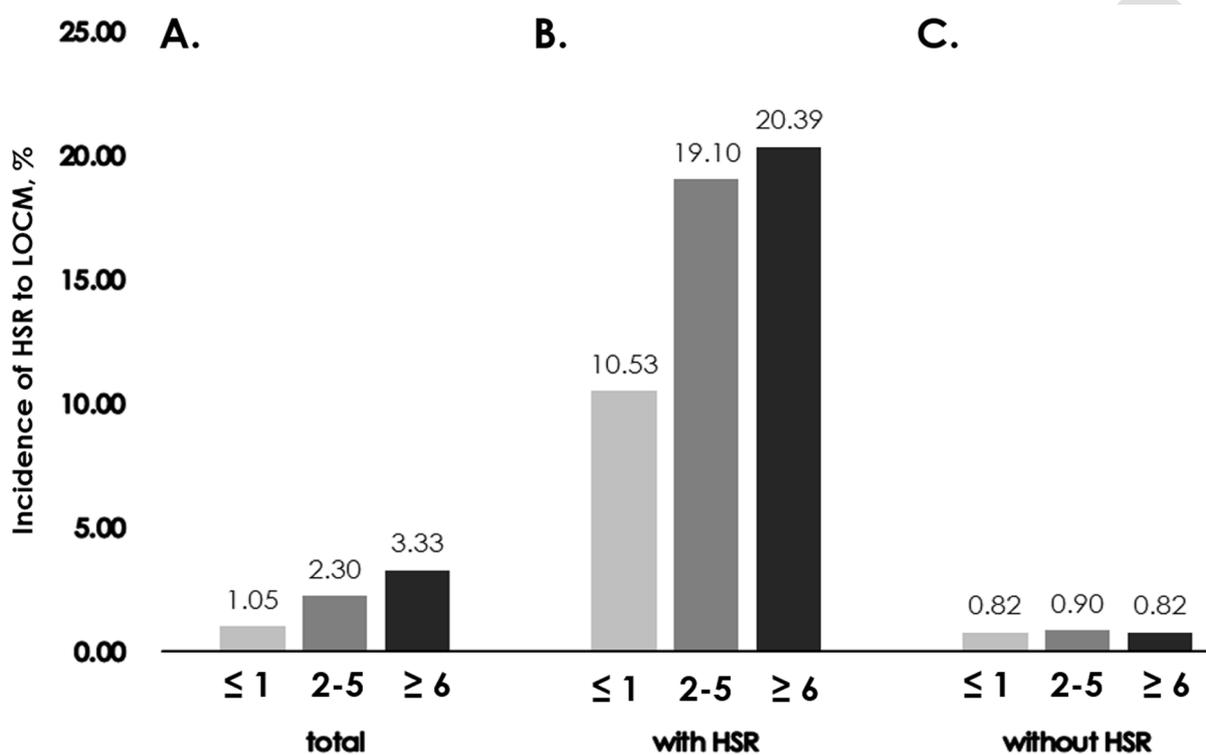


Figure 2. The incidence of iodinated contrast media hypersensitivity showed gradually increasing trend as the number of previous exposure increase ( $p < 0.001$ ).



A, total; B, with previous history of LCM hypersensitivity; C, without previous history of LOCM hypersensitivity

\*The incidence rate was calculated by dividing the number of all patients by the number of patients with LOCM hypersensitivity.

LOCM, low-osmolar iodinated contrast media