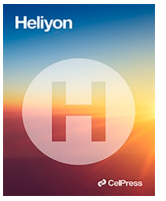
Heliyon 9 (2023) e21694

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Thyroid dysfunction associated with iodine-contrast media: A real-world pharmacovigilance study based on the FDA adverse event reporting system

Lu Huang [a,b,c,1], Yan Luo [a,b,d,1], Zhen-Lin Chen [c], Zhi-Yun Yang [e,f,**], Yue Wu [a,b,*]

[a] *Department of Pharmacy, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China*
[b] *Personalized Drug Therapy Key Laboratory of Sichuan Province, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China*
[c] *Department of Pharmacy, People's Hospital of Fushun County, Fushun, China*
[d] *Department of Pharmacy, Chengdu Seventh People's Hospital, Chengdu, China*
[e] *Department of Pharmacy, Xiangya Hospital, Central South University, Changsha, China*
[f] *National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Institute for Rational and Safe Medication Practices, Central South University, Changsha, China*

A B S T R A C T

Objective: To comprehensively analyze characteristics of thyroid dysfunction associated with iodine contrast media (ICM) based on data from the FDA adverse event reporting system (FAERS).
Methods: Disproportionate analysis was employed to identify signals of thyroid dysfunction caused by ICM, and descriptive analysis was performed to examine the clinical characteristics of reported cases involving ICM-related thyroid dysfunctions.
Results: A total of 83 adverse event reports were identified, documenting thyroid dysfunctions associated with ICM agents. Treatment with ICM was significantly associated with higher reporting of hypothyroidism ([ROR] = 2.21, 95 % CI: 1.59–3.08; IC_{025} = 0.58) and hyperthyroidism (ROR = 3.49, 95 % CI: 2.37–5.13; IC_{025} = 1.14). Among the six ICM agents investigated, iodixanol demonstrated the highest signal strength in both hypothyroidism (ROR = 9.47) and hyperthyroidism (ROR = 5.44). Hypothyroidism and hyperthyroidism almost occurred in the first 30 days after ICM administration (76.9 % and 70 % of patients, respectively). Furthermore, the proportion of severe outcomes in hyperthyroidism was significantly higher than that in hypothyroidism (12/26 vs. 2/35, P = 0.009).
Conclusion: The present study highlights the varying risks of thyroid dysfunction associated with different ICM agents, with iodixanol exhibiting the highest signal intensity. Hypothyroidism and hyperthyroidism associated with ICM generally manifest within the first month following administration. Consequently, monitoring of thyroid function during this period is strongly recommended for ICM agents presenting higher risk profiles.

1. Introduction

Iodine contrast media (ICM) is a water-soluble radiocontrast agent containing iodine, utilized in radiological examinations to enhance the visualization of vascular structures and organs [1]. With the rapid growth of radiology applications, particularly in computed tomography and vascular interventional surgery, the use of ICM has experienced a significant increase. Global statistics

* Corresponding author. No. 32, Section 2, 1st Ring Road, Chengdu, Sichuan Province, 610072, China.
** Corresponding author. No. 87, Xiangya Road, Changsha, Hunan Province, 410008, China.
E-mail addresses: yangzyun@outlook.com (Z.-Y. Yang), 867099199@qq.com (Y. Wu).
[1] These two authors contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2023.e21694
Received 12 July 2023; Received in revised form 9 September 2023; Accepted 25 October 2023
Available online 26 October 2023

indicate an annual administration of over 75 million doses of ICM [2]. Therefore, the safety of ICM has become an increasingly important concern. In June 2021, the European Thyroid Association released guidelines for managing ICM-induced thyroid dysfunction, aiming to ensure their safe usage in clinical settings [3].

Thyroid dysfunction, including hyperthyroidism and hypothyroidism, may occur as a result of the elevated iodine concentration present in ICM, especially in patients with specific risk factors [4]. Acknowledging the potential risks, the U.S. Food and Drug Administration (FDA) implemented a new warning in March 2022, highlighting the importance of monitoring thyroid function, particularly in children aged three years or younger, during the administration of ICM injections [5]. Nevertheless, the existing studies on the impact of ICM on thyroid function remain limited, predominantly confined to clinical trials or observational studies, lacking comprehensive real-world data for analyzing ICM-related thyroid dysfunction and comparing the variances among different ICM agents.

The FDA Adverse Event Reporting System (FAERS) represents one of the largest pharmacovigilance databases encompassing real-world data on adverse event (AE) reports [6,7]. By harnessing the extensive sample size available within the FAERS, it is possible to enhance the detection of adverse drug reactions, including the identification of rare potential AEs. Additionally, the FAERS allows for the acquisition of clinical characteristics pertaining to specific AEs, such as time to onset and patients outcomes. Under the circumstances, our study aims to employ a disproportionality analysis based on the data from the FAERS to comprehensively evaluate thyroid dysfunction associated with ICM and describe the clinical characteristics of reported cases involving ICM-related thyroid dysfunctions. The findings from this study will serve as valuable references for the safe and effective utilization of ICM.

2. Methodology

2.1. Study design and data sources

We conducted a retrospective, observational pharmacovigilance study to investigate the association between ICM and thyroid dysfunction. The study utilized the entire AE reports contained within the FAERS database, ranging from the first quarter of 2004 (2004 Q1) to the first quarter of 2023 (2023 Q1). In order to acquire the relevant AE report data, ICM agents, including iopromide (Ultravist), iohexol (Omnipaque), iopamiro (Iopamiro), ioversol (Optiray), iodixanol (Visipaque), and iotrolan (Isovist), were employed as keywords.

The FAERS database represents a comprehensive, publicly accessible spontaneous reporting system. It incorporates global information concerning drug-related AEs and medication errors, reported by healthcare professionals, patients, and pharmaceutical companies within the United States and other regions worldwide [8,9]. The FAERS database undergoes regular quarterly updates and can be accessed online at https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html. In addition, all reported AEs within the FAERS database are coded using preferred term (PT) codes from the Medical Dictionary for Regulatory Activities (MedDRA). To ensure the inclusion of clinically relevant thyroid dysfunctions, PTs associated with all thyroid dysfunctions within the MedDRA (version 24.0) were obtained based on the system organ class (SOC) of “Endocrine disorders".

2.2. Data processing procedure

The FAERS database encompasses a diverse array of data sets, including demographic and administrative information (DEMO), drug information (DRUG), adverse events (REAC), patient outcomes (OUTC), reporting sources (RPSR), treatment start and end dates (THER), and dosing indications (INDI) [10]. All data within the FAERS database is stored in either ASCII or XML format. In our study, we retrieved the ASCII data format for analysis. To ensure data integrity and avoid duplication, we followed the recommendations provided by the FDA [11]. Specifically, we employed a de-duplication process based on two criteria. Firstly, when the CASEID (the unique identifier for FAERS cases) was the same, we selected the most recent FDA_DT (the date on which the case was received by the FDA). Secondly, in cases where both CASEID and FDA_DT were identical, we selected the report with the higher PRIMARYID (the unique number assigned to FAERS reports) to prevent redundancy and maintain the most comprehensive and up-to-date information for our analysis.

2.3. Signal mining

In this study, we employed disproportionality analysis to assess the specific reporting patterns of suspected target thyroid dysfunctions AEs associated with ICM compared to other drugs within the FAERS database. Disproportionality can be measured using either the information component (IC) or the reporting odds ratio (ROR) when utilizing the full database as a comparator. To ensure robust and reliable outcomes, a statistical shrinkage transformation model was implemented [12]. This approach, recommended by the World Health Organization Uppsala Monitoring Center, aims to mitigate false-negative adverse signals. The formula utilized for the statistical shrinkage transformation is as follows:

$$IC = Log_2\left(\frac{N_{observed} + 0.5}{N_{expected} + 0.5}\right)$$

$$N_{expected} = \frac{N_{drug} * N_{event}}{N_{total}}$$

where $N_{expected}$ is the number of AE records expected for the ICM. $N_{observed}$ is the number of thyroid dysfunctions AEs records for the ICM. N_{drug} is the number of all AE reports associated with ICM. N_{event} is the number of thyroid dysfunctions AEs reported in the database. N_{total} is the number of all AE reports for all drugs in the database. The IC_{025} represents the lower boundary of the 95 % credibility interval for the IC, which serves as a statistical measure. Traditionally, a positive value exceeding zero is considered the threshold for detecting signals. In our analysis, we also estimated the disproportionality of thyroid dysfunction AEs based on different variable ICM regimens by calculating the ROR along with its corresponding 95 % confidence interval (95 % CI). A lower limit of the 95 % CI (ROR_{05}) equals to or greater than 1 was deemed indicative of a significant signal.

$$ROR = \frac{N_{observed} + 0.5}{N_{expected} + 0.5}$$

2.4. Descriptive analysis

A comprehensive descriptive analysis was conducted to summarize the clinical characteristics of reports documenting ICM-related thyroid dysfunctions within the FAERS database, including gender, country, outcome, the date of the case received by the FDA, ICM therapy, report type, and other relevant clinical features. The onset time of ICM-related thyroid dysfunctions was derived by subtracting the event start time (EVENT_DT) from the therapy start time (START_DT). Reports containing erroneous or inaccurate entries, such as EVENT_DT preceding START_DT or missing data, were excluded from the analysis. Furthermore, the proportion of severe outcomes (including death, disability, life-threatening events, and hospitalization) was examined, with a specific focus on reports associated with fatal outcomes linked to thyroid dysfunction events.

2.5. Statistical analysis

To compare the onset time of ICM-related thyroid dysfunctions, we employed the nonparametric Wilcoxon rank sum test. The Chi-square test or Fisher's exact test was utilized for analyzing between-group differences in categorical variables and conducting statistical tests in the disproportional analysis. $P < 0.05$ was considered statistically significant, and all statistical tests were two-tailed. All statistical analysis and visualizations were conducted using R software (version 4.3) and GraphPad Prim 9.

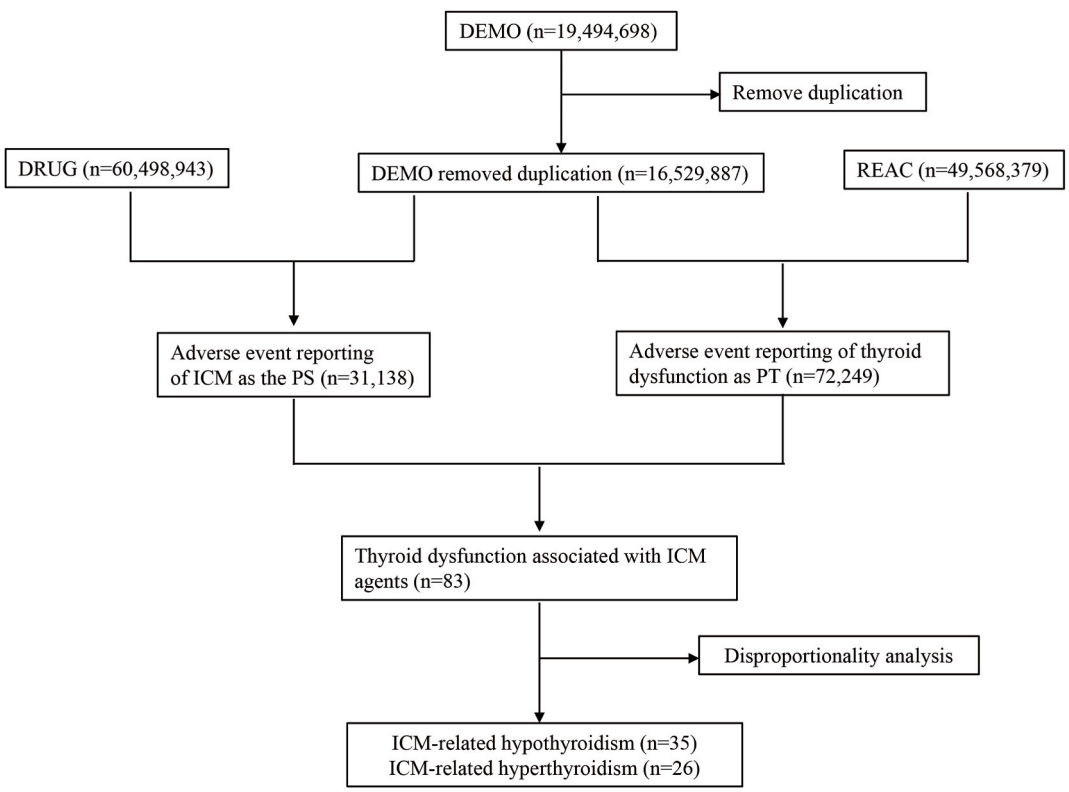


Fig. 1. The flow diagram of selecting ICM-related thyroid dysfunctions from the FAERS database.

3. Results

3.1. Data selection

In this study, a comprehensive analysis of AE reports was conducted using data retrieved from the FAERS database ranging from 2004Q1 to 2023Q1 (Fig. 1). Initially, a total of 19,494,698 AE reports were obtained, which were subsequently deduplicated, resulting in 16,529,887 unique AE reports. Among these, 31,138 reports were specifically associated with iodine contrast media (ICM) as the primary suspected (PS) drug. Further analysis revealed that out of a total of 49,568,379 AE recorded in the database, 72,249 were related to thyroid dysfunctions. Subsequently, 83 AE reports, encompassing 14 preferred terms, were identified as thyroid dysfunction AEs associated with ICM agents and were subjected to disproportionality analysis. The distribution of thyroid dysfunction AEs reported for different ICM agents is presented in Table 1.

The results demonstrated a significant increase in four types of thyroid dysfunction AEs following treatment with ICM agents compared to the reporting frequency in the FAERS database. Specifically, ICM treatment exhibited higher reporting rates for hypothyroidism (24759 reports for the full database vs 35 for ICM agents, ROR = 2.21 [95%CI, 1.59–3.08]; IC_{025} = 0.58; Table 1), hyperthyroidism (11292 vs 26, ROR = 3.49 [2.37–5.13]; IC_{025} = 1.14), thyrotoxic crisis (746 vs 4, ROR = 4.64 [1.74–12.41]; IC_{025} = 0.45), and primary hypothyroidism (136 vs 4, ROR = 7.69 [2.84–20.78]; IC_{025} = 1.17) when compared to the reporting rates of these AEs in the entire FAERS database. However, other thyroid dysfunction AEs such as Graves' disease, thyroid disorder, autoimmune thyroiditis, adrenal insufficiency, goiter, and thyroiditis did not exhibit a higher prevalence in patients who received ICM when compared to the full database (Table 1). Given the rarity of thyrotoxic crisis and primary hypothyroidism (n < 5), our focus was primarily directed towards hypothyroidism and hyperthyroidism to investigate the presence of increased signals for these toxicities across various ICM agents and to describe the associated clinical characteristics.

3.2. Clinical characteristics

We have provided a detailed description of the clinical characteristics associated with hypothyroidism (n = 35) and hyperthyroidism (n = 26) cases in patients who received ICM agents, as summarized in Table 2. The majority of reports concerning these two ICM-related thyroid dysfunctions originated from European countries (91.4 % and 80.8 %), followed by North America (5.7 % and 15.4 %). Notably, the reliability of the AE reports appears to be high, given the substantial proportion of reports submitted by healthcare professionals (97.1 % and 84.6 %). Furthermore, it is worth noting that the AE reports primarily focus on recent years,

Table 1
The thyroid dysfunction AEs reported with different ICM reagents versus those reported in the full database from FAERS, from 2004 Q1 to 2023 Q1.

	The number of AEs reported with ICM agents (n = 31,138)	The total number of AEs in the FARES database (n = 49,568,379)	IC (IC_{025})	ROR (95 % CI)
Hypothyroidism	35	24759	1.14 (0.58)	2.21 (1.59–3.08)
Hyperthyroidism	26	11292	1.80 (1.14)	3.49 (2.37–5.13)
Thyrotoxic crisis	4	746	2.21 (0.45)	4.64 (1.74–12.41)
Primary hypothyroidism	4	136	2.94 (1.17)	7.69 (2.84–20.78)
Graves' disease	3	2326	0.83 (−1.24)	1.78 (0.57–5.54)
Thyroid disorder	2	12390	−1.73 (−4.32)	0.30 (0.08–1.21)
Autoimmune thyroiditis	2	2894	0.11 (−2.48)	1.08 (0.27–4.31)
Adrenal insufficiency	1	8204	−1.91 (−5.70)	0.27 (0.04–1.88)
Goitre	1	3559	−0.87 (−4.65)	0.55 (0.08–3.89)
Thyroiditis	1	2133	−0.30 (−4.08)	0.81 (0.11–5.79)
Adrenal disorder	1	1512	0.05 (−3.73)	1.03 (0.15–7.35)
Adrenocortical insufficiency acute	1	1275	0.20 (−3.58)	1.15 (0.16–8.19)
Parathyroid disorder	1	678	0.70 (−3.09)	1.62 (0.23–11.51)
Hyperadrenocorticism	1	262	1.17 (−2.61)	2.26 (0.32–16.08)

Note: ICM agents refers to any AEs reported for treatment with iopromide, iohexol, iopamiro, ioversol, iodixnaol, and iotrolan. A positive IC_{025} value ($IC_{025} > 0$) is the traditional threshold used in statistical signal detection. ICM, iodine contrast media; IC, information component; IC_{025}, lower limit of a 95 % credibility interval for the IC; ROR, reporting odds ratio; 95 % CI, the 95 % confidential interval for the ROR.

Table 2
Clinical characteristics of patients with ICM-associated hypothyroidism and hyperthyroidism obtained from the FAERS.

	Hypothyroidism (n = 35)	Hyperthyroidism (n = 26)
Gender		
Male	1 (2.9 %)	13 (50 %)
Female	2 (5.7 %)	7 (26.9 %)
Missing or unknown	32 (91.4 %)	6 (23.1 %)
Reporters		
Health-care professional	34 (97.1 %)	22 (84.6 %)
Non-health-care professional	1 (2.9 %)	2 (7.6 %)
Missing or unknown	0 (0 %)	2 (7.6 %)
Reporting regions		
North America	2 (5.7 %)	4 (15.4 %)
Europe	32 (91.4 %)	21 (80.8 %)
Asia	1 (2.9 %)	0 (0 %)
Not specified	0 (0 %)	1 (3.8 %)
Reporting year		
2020–2023	33 (94.3 %))	7 (26.9 %)
2015–2019	2 (5.7 %)	11 (42.3 %)
2010–2014	0 (0 %)	7 (26.9 %)
2004–2009	0 (0 %)	1 (3.8 %)
Outcomes		
Death (DE)	1 (2.9 %)	2 (7.6 %)
Hospitalization (HO)	1 (2.9 %)	9 (34.6 %)
Disability (DS)	0 (0 %)	1 (3.8 %)
Others (OT)	32 (91.4 %)	14 (53.8 %)
Missing or unknown	1 (2.9 %)	1 (3.8 %)
ICM regimens		
Iodixanol	30 (85.7 %)	9 (34.6 %)
Iohexol	2 (5.7 %)	10 (38.5 %)
Iopamiro	2 (5.7 %)	0 (0 %)
Iopromide	0 (0 %)	4 (15.4 %)
Ioversol	1 (2.9 %)	3 (11.5 %)
Iotrolan	0 (0 %)	0 (0 %)
Time to onset		
Median (IQR, days)	8 (5.25–28.5); n = 26	13 (2.75–80.25); n = 10
0–30 days	20/26 (76.9 %)	7/10 (70.0 %)
31–90 days	1/26 (3.8 %)	0/10 (0 %)
91–180 days	0/26 (0 %)	3/10 (30.0 %)
>180 days	5/26 (19.2 %)	0/10 (0 %)

Note: Data are n (%), n/N (%), mean (SD; range), or median (IQR; range). ICM, iodine contrast media; FAERS, the FDA Adverse Event Reporting System; IQR, interquartile range.

which may be attributed to the growing utilization of ICM agents and an increased emphasis on AE reporting.

Among the six different ICM agents investigated, iotrolan did not yield any reports of hypothyroidism or hyperthyroidism due to its limited use. However, among the remaining five ICM agents, AE signals of hypothyroidism were detected for iohexol, iopamiro, ioversol, and iodixanol, with iodixanol accounting for the majority of reports (30 [85.7 %] out of 35 hypothyroidism cases) and exhibiting the strongest signal (ROR = 9.47 [95%CI: 6.61–13.56]; see Fig. 2). While AE signals of hyperthyroidism were observed for iodixanol (9 [34.6 %] out of 26 hyperthyroidism cases), iohexol (10 [38.5 %]), iopromide (4 [15.4 %]), and ioversol (3 [11.5 %]). Consistent with hypothyroidism, iodixanol-related hyperthyroidism demonstrated the strongest signal (ROR = 5.44 [95%CI: 2.83–10.46]; see Fig. 2).

3.3. Time to onset

Among the AE reports associated with ICM, a total of 26 reports provided detailed information regarding the time-to-onset of hypothyroidism, while 10 reports provided such information for hyperthyroidism. Notably, both thyroid dysfunction AEs manifested shortly after the administration of ICM, with a median time to onset of 8 days (interquartile range [IQR]: 5.25–28.5) for hypothyroidism and 13 days (IQR: 2.75–80.25) for hyperthyroidism. The specific occurrence times and the distribution of reports across different time periods are visually depicted in Fig. 3. It is evident that the occurrence of hypothyroidism and hyperthyroidism predominantly took place within the first 30 days following ICM use, with 76.9 % and 70 % of patients experiencing these AEs, respectively, particularly within the initial 10 days. However, there was no significant difference in the time to onset between these two thyroid dysfunction AEs (P = 0.986; Fig. 3).

3.4. Outcome

Among the 35 patients who developed hypothyroidism following ICM treatment (37 reported outcomes), there were one death

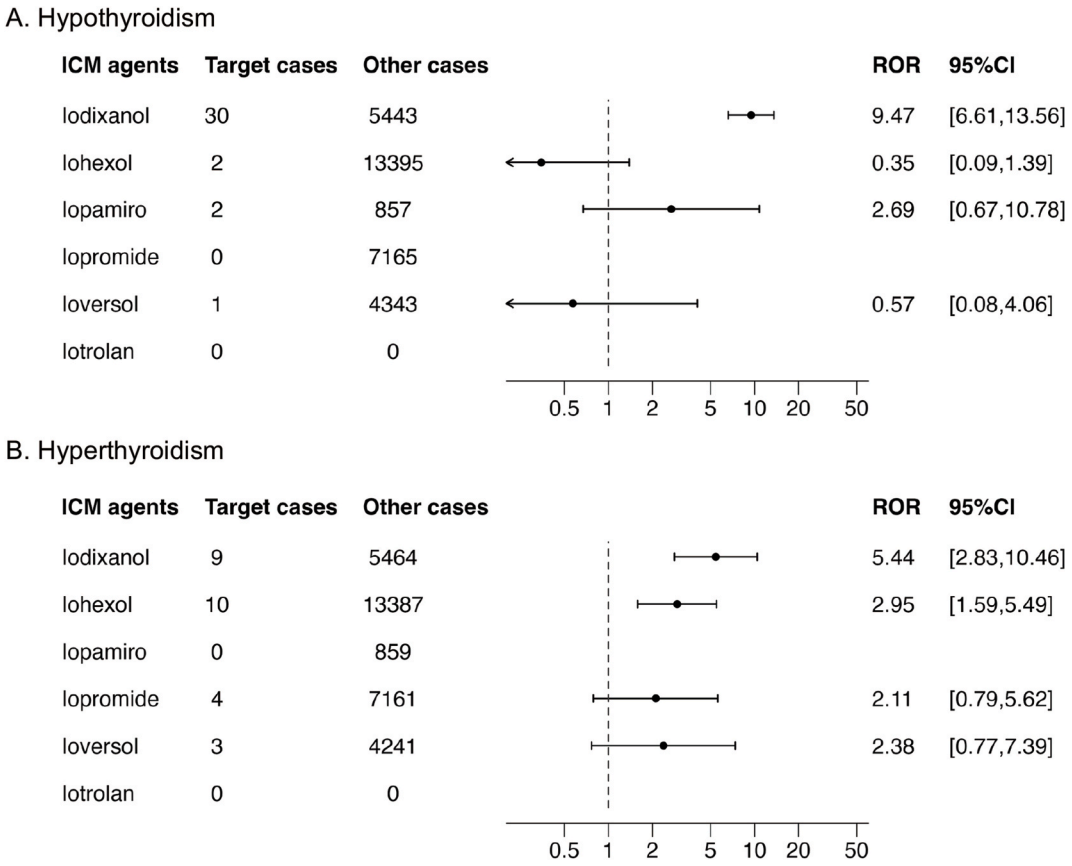


Fig. 2. The forest plots of disproportionality of different ICM agents-related hypothyroidism (A) and hyperthyroidism (B). ROR, reporting odds ratio; RORL, the lower limit of 95 % confidence interval of ROR; RORU, the upper limit of 95 % confidence interval of ROR.

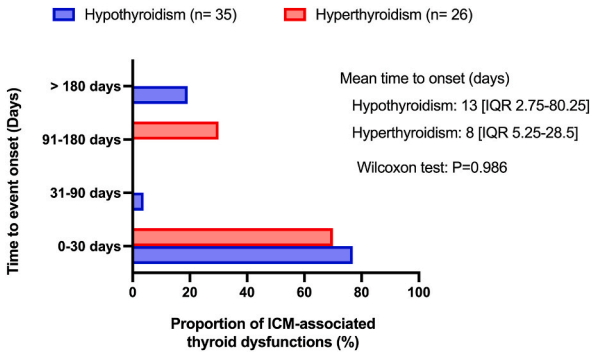


Fig. 3. The time to event onset for hypothyroidism and hyperthyroidism reported in individual case safety reports from the FAERS. Statistical tests were conducted using the nonparametric Wilcoxon rank sum test.

case. It occurred in an 83-year-old female patient who had been administered ioversol. Despite being hospitalized, the patient's condition deteriorated, resulting in fatality. The majority of patients with hypothyroidism experienced outcomes classified as "other" (OT, n = 32 [91.4 %], see in Table 2). Regarding the 26 patients who developed hyperthyroidism (32 reported outcomes), two patients died due to the treatment of iodixanol and iopromide, respectively. Additionally, nine patients required hospitalization (34.6 %). Although no statistically significant difference was observed in the proportion of deaths reported between hypothyroidism and hyperthyroidism (P = 0.823), it is worth noting that the proportion of severe outcomes was significantly higher in cases of hyperthyroidism compared to hypothyroidism (12/26 vs. 2/35, P = 0.009, Table 2).

4. Discussion

As the commonly used drugs in imaging examination, the safety issue of ICM has raised significant clinical apprehension and garnered considerable attention, particularly due to their increased usage in recent years. Since the initial alert by the FDA in 2015 regarding the risk of hypothyroidism following ICM administration [13], there has been growing concern regarding the impact of ICM on thyroid function. Rhee et al. conducted a nested case-control study of patients treated with ICM agents between January 1, 1990 and June 30, 2010. They found a statistically significant association between ICM exposure and incident overt hyperthyroidism and hypothyroidism [14]. Likewise, a 6-year retrospective cohort study in Asian populations revealed that ICM exposure was associated with an increased risk of thyroid dysfunction [15]. However, there is still a lack of studies to analyze the variations in thyroid dysfunction risk and evaluate differences among various ICM agents in causing thyroid dysfunction based on the worldwide large-scale data from the real-world settings. In this study, we obtained all AE reports associated with ICM agents from the FAERS database to conduct a comprehensive analysis of the risk posed by six commercially available ICM agents. Moreover, we described the demographic characteristics of hyperthyroidism and hypothyroidism associated with ICM, along with assessing the time-to-onset and patient outcomes.

Iodine is an essential micronutrient for thyroid hormone synthesis [16,17]. It enters thyroid follicular and parafollicular cells through the sodium-iodide symporter (NIS) on the cell membrane, where it participates in thyroid hormone production [18,19]. However, acute iodine excess from ICM exposure can disrupt thyroid function and lead to hyper- or hypothyroidism [3]. The primary mechanisms underlying ICM-induced hyperthyroidism are the Jod-Basedow effect and selective NIS inhibition in thyroid cells. For hypothyroidism, the main mechanism is persistent Wolff-Chaikoff effect [20]. Under normal conditions, the thyroid can escape Wolff-Chaikoff inhibition and restore hormone synthesis. Most studies indicate this escape involves reduced NIS expression, lowering intracellular iodine levels. However, acute ICM-mediated iodine excess during computed tomography can prevent escape from the Wolff-Chaikoff effect in thyroid cells, increasing hypothyroidism risk due to inadequate hormone production [21].

In our study, AE reports of thyroid dysfunction were identified for six commonly used ICM agents, with four agents exhibiting positive signals for hypothyroidism and hyperthyroidism, respectively. Notably, iodixanol, the third-generation hypotonic ICM, demonstrated the highest signal strength for both hypothyroidism (ROR = 9.47) and hyperthyroidism (ROR = 5.44). Regarding osmotic pressure, no association between osmotic pressure and thyroid dysfunction was observed. Conversely, iodixanol, as the only isotonic ICM, exhibited the highest signal intensity, likely due to its higher viscosity and increased iodine loading as a dimeric ICM [22]. Despite iodixanol being widely used in radiology due to its lower risk of cardiac and renal adverse reactions and reduced injection discomfort, a retrospective study found a higher overall incidence of AEs associated with iodixanol compared to other ICM agents ($P < 0.01$) [23]. Our study also identified a higher risk of thyroid dysfunction associated with iodixanol. Therefore, careful attention should be given to the safety concerns regarding the clinical application of iodixanol.

Our study revealed that the majority of ICM-related thyroid dysfunction cases manifested within the first 30 days following initial dosing, particularly within the initial 10 days. This temporal pattern aligns with the transient nature of the Wolff-Chaikoff effect, which typically dissipates within approximately two weeks [24]. Consequently, thyroid dysfunction predominantly arises within the initial 30 days, underscoring the criticality of thyroid monitoring during this timeframe. Consistent with these findings, the FDA recommends thyroid follow-up evaluations for newborns and children aged three years or younger within three weeks of receiving ICM. Based on our results, although the majority of cases can be detected within the first ten days, extending monitoring to one month for high-risk populations is advisable.

Within our study, three fatalities associated with hyperthyroidism and hypothyroidism were reported. While no direct causal relationship with ICM could be established, these occurrences emphasize the importance of judicious selection of ICM type and dosage for infants and elderly individuals with complex underlying conditions. Furthermore, the proportion of severe outcomes in hyperthyroidism cases was significantly higher than that in hypothyroidism cases (48 % vs. 5.8 %, $P < 0.01$). This discrepancy is likely attributed to the higher prevalence of elderly patients among those with hyperthyroidism. Moreover, prolonged hyperthyroidism can exert increased cardiovascular strain and exacerbate preexisting heart conditions, including heart failure [25,26].

4.1. Limitations

There are several limitations in our study. Firstly, the FAERS database, being a spontaneous reporting system, inherently possesses certain limitations such as nonuniform data formats, data duplication, and missing data due to multiple data sources. Secondly, it is important to note that the actual number of thyroid dysfunction cases may be underestimated in this study, as mild thyroid AEs often go unreported by physicians and patients to the FAERS. Thirdly, due to the lack of information on the total number of patients receiving ICM agents, it is not possible to determine the exact incidence of thyroid dysfunction. Fourthly, while the signals identified in this study demonstrate a statistical correlation between ICM and the risk of thyroid dysfunction, it is essential to recognize that this does not imply a biological causative relationship, thus necessitating further validated investigations in future studies.

5. Conclusions

In conclusion, the findings of this study suggest varying risks of thyroid dysfunction associated with different ICM agents, with iodixanol exhibiting the highest signal intensity. The occurrence of ICM-related hypothyroidism and hyperthyroidism generally manifest within the initial month following treatment, highlighting the importance of monitoring thyroid function during this timeframe, particularly for ICM agents posing a higher risk. Although thyroid dysfunction AEs are typically non-fatal, it is crucial to note that patients with hyperthyroidism may experience severe outcomes, warranting increased clinical attention.

Authors' contributions

Conceptualization, Z.Y. Yang, and Y. Wu.; collected and analysis the data, L. Huang, Y. Luo, and Z.L. Chen; writing-original draft manuscript, L. Huang and Y. Luo; figure preparation, L. Huang and Y. Luo; final editing, L. Huang, Y. Luo, Z.L. Chen, and Y. Wu. All authors have read and approved the submission of the manuscript.

Funding statement

This work was funded by the National Key Research and Development Program of China (2020YFC2005506) and Key Research and Development Program of Science and Technology Department of Sichuan Province (2019YFS0514).

Data availability statement

All the original data of this study are available with publication from the corresponding authors upon reasonable request.

Declaration of competing interest

The authors have declared no competing interest.

References

[1] A.-L. Faucon, G. Bobrie, O. Clément, Nephrotoxicity of iodinated contrast media: from pathophysiology to prevention strategies, Eur. J. Radiol. 116 (2019) 231–241.
[2] N. Ding, X. Liu, A. Meng, X. Zhao, G. Ma, W. Han, P. Dong, J. Li, J. Zhou, Manifesting viscosity changes in lipid droplets during iodined CT contrast media treatment by the real-time and in situ fluorescence imaging, Chin. Chem. Lett. 34 (2023), 107745.
[3] T. Bednarczuk, T.H. Brix, W. Schima, G. Zettinig, G.J. Kahaly, 2021 European Thyroid Association guidelines for the management of iodine-based contrast media-induced thyroid dysfunction, Eur. Thyroid J. 10 (2021) 269–284.
[4] J. Manso, I. Piva, S. Censi, C. Clausi, M. Bardi, B. Schiavon, I. Merante Boschin, F. Tona, C. Mian, Safety and efficacy of prophylactic treatment for hyperthyroidism induced by iodinated contrast media in a high-risk population, Front. Endocrinol. 14 (2023), 1154251.
[5] A. Baioumi, R. Burrows, R. Hayward, R. Pryce, Contrast Media-Induced Hypothyroidism, Bioscientifica), 2022.
[6] Y. Shu, Y. Ding, B. Dai, Q. Zhang, A real-world pharmacovigilance study of axitinib: data mining of the public version of FDA adverse event reporting system, Expet Opin. Drug Saf. 21 (2022) 563–572.
[7] H. Guo, B. Wang, S. Yuan, S. Wu, J. Liu, M. He, J. Wang, Neurological adverse events associated with esketamine: a disproportionality analysis for signal detection leveraging the FDA adverse event reporting system, Front. Pharmacol. 13 (2022), 849758.
[8] Y. Xiao, Y. Chen, Y. Huang, Y. Xiao, Atypical femur fracture associated with common anti-osteoporosis drugs in FDA adverse event reporting system, Sci. Rep. 13 (2023), 10892.
[9] M.M. Dhodapkar, X. Shi, R. Ramachandran, E.M. Chen, J.D. Wallach, J.S. Ross, Characterization and corroboration of safety signals identified from the US food and drug administration adverse event reporting system, 2008-19: cross sectional study, BMJ 379 (2022).
[10] J. Peng, H. Wang, Z. Liu, Z.-L. Xu, M.-X. Wang, Q.-M. Chen, M.-L. Wu, X.-L. Ren, Q.-H. Liang, F.-P. Liu, Real-world study of antiresorptive-related osteonecrosis of jaw based on the US food and drug administration adverse event reporting system database, Front. Pharmacol. 13 (2022), 1017391.
[11] X. Li, P. Ndungu, S.B. Taneja, M.R. Chapin, S.B. Egbert, K. Akenapalli, M.F. Paine, S.L. Kane-Gill, R.D. Boyce, An evaluation of adverse drug reactions and outcomes attributed to kratom in the US food and drug administration adverse event reporting system from January 2004 through September 2021, Clin. Transl. Sci. 16 (2023) 1002–1011.
[12] O. Caster, K. Juhlin, S. Watson, G.N. Norén, Improved statistical signal detection in pharmacovigilance by combining multiple strength-of-evidence aspects in vigiRank: retrospective evaluation against emerging safety signals, Drug Saf. 37 (2014) 617–628.
[13] T.J. Dietrich, R. Sutter, J.M. Froehlich, C.W. Pfirrmann, Particulate versus non-particulate steroids for lumbar transforaminal or interlaminar epidural steroid injections: an update, Skeletal Radiol. 44 (2015) 149–155.
[14] C.M. Rhee, I. Bhan, E.K. Alexander, S.M. Brunelli, Association between iodinated contrast media exposure and incident hyperthyroidism and hypothyroidism, Arch. Intern. Med. 172 (2012) 153–159.
[15] E. Kornelius, J.-Y. Chiou, Y.-S. Yang, C.-H. Peng, Y.-R. Lai, C.-N. Huang, Iodinated contrast media increased the risk of thyroid dysfunction: a 6-year retrospective cohort study, J. Clin. Endocrinol. Metabol. 100 (2015) 3372–3379.
[16] M.C. Opazo, I. Coronado-Arrázola, O.P. Vallejos, R. Moreno-Reyes, C. Fardella, L. Mosso, A.M. Kalergis, S.M. Bueno, C.A. Riedel, The impact of the micronutrient iodine in health and diseases, Crit. Rev. Food Sci. Nutr. 62 (2022) 1466–1479.
[17] V. Triggiani, E. Tafaro, V.A. Giagulli, C. Sabbà, F. Resta, B. Licchelli, E. Guastamacchia, Role of iodine, selenium and other micronutrients in thyroid function and disorders, Endocr. Metab. Immune Disord. - Drug Targets 9 (2009) 277–294.
[18] D.P. Carvalho, C. Dupuy, Thyroid hormone biosynthesis and release, Mol. Cell. Endocrinol. 458 (2017) 6–15.
[19] M. Soundarrajan, P.A. Kopp, Thyroid hormone biosynthesis and physiology, Thyroid Disease and Reproduction: A Clinical Guide to Diagnosis and Management (2019) 1–17.
[20] A.M. Leung, L.E. Braverman, Iodine-induced thyroid dysfunction, Curr. Opin. Endocrinol. Diabetes Obes. 19 (2012) 414.
[21] S.Y. Lee, C.M. Rhee, A.M. Leung, L.E. Braverman, G.A. Brent, E.N. Pearce, A review: radiographic iodinated contrast media-induced thyroid dysfunction, J. Clin. Endocrinol. Metabol. 100 (2015) 376–383.
[22] P.A. McCullough, M.E. Bertrand, J.A. Brinker, F. Stacul, A meta-analysis of the renal safety of isosmolar iodixanol compared with low-osmolar contrast media, J. Am. Coll. Cardiol. 48 (2006) 692–699.
[23] Q.-l. Chen, X.-y. Zhao, X.-m. Wang, N. Lv, L.-l. Zhu, H.-m. Xu, Q. Zhou, Retrospective analysis of non-laboratory-based adverse drug reactions induced by intravenous radiocontrast agents in a Joint Commission International-accredited academic medical center hospital in China, Therapeut. Clin. Risk Manag. (2017) 565–573.
[24] A. de Carmo Campos, I.C. Carvalho, S. Sarmento, T. Fonseca, I. Carvalho, Iodine-induced hypothyroidism after chemoembolization with ethiodized oil: a case of failure to escape from wolff-chaikoff effect (WCE), Cureus 15 (2023).
[25] S. Razvi, A. Jabbar, A. Pingitore, S. Danzi, B. Biondi, I. Klein, R. Peeters, A. Zaman, G. Iervasi, Thyroid hormones and cardiovascular function and diseases, J. Am. Coll. Cardiol. 71 (2018) 1781–1796.
[26] A. Navarro-Navajas, J.D. Cruz, N. Ariza-Ordoñez, H. Giral, J. Palmezano, A. Bolívar-Mejía, Q. Santana, R. Fernandez, L. Durango, C. Saldarriaga, Cardiac manifestations in hyperthyroidism, Rev. Cardiovasc. Med. 23 (2022) 136.