scientific reports

Check for updates

OPEN

Exploring the dark side of diagnostic dyes with a focus on Indocyanine green's adverse reactions

Yan Jiao[1], Yahui Liu[1] & Meng Jin[2,3]✉

Indocyanine green (ICG) is a diagnostic dye commonly used in medical imaging and liver function monitoring. Given its widespread use, there is a need for detailed evaluations of its adverse drug reactions in real-world settings. As the comprehensive overview of its safety profile is very limited, this study aimed to analyze the adverse events (AEs) associated with ICG using data from the Food and Drug Administration Adverse Event Reporting System (FAERS). Data between 2004Q1 and 2023Q4 were extracted from the FAERS database. Signal detection was performed using various disproportionality analysis algorithms, including reporting odds ratio (ROR), proportional reporting ratio, Bayesian confidence propagation neural network, and multiitem gamma Poisson shrinker. During the study period, a total of 62 ICG-related AEs were reported in the FAERS database. Significant clinical adverse reactions included anaphylactic shock (ROR: 92.10, 95% confidence interval (CI): 37.71-224.96), procedural hypotension (ROR: 1397.27, 95% CI: 443.31-4404.08), and urticaria (ROR: 10.88, 95% CI: 4.02–29.42). This study provides valuable insights into the safety profile of ICG, highlighting the need for further monitoring to ensure its safe clinical use in clinical practice. Ongoing pharmacovigilance and large-scale studies are warranted to fully understand the potential risks associated with ICG.

Keywords Indocyanine green, Adverse drug reactions, FAERS database, Pharmacovigilance, Signal detection

Indocyanine green (ICG) is a non-toxic, water-soluble, tricarbocyanine dye approved by the United States Food and Drug Administration (FDA) for several medical applications due to its unique properties (Figure S1). It absorbs near-infrared light and emits it at a longer wavelength, making it ideal for various diagnostic and surgical procedures where visualization of blood flow, lymphatic drainage, or tissue perfusion is crucial[1–3]. In addition, ICG-guided real-time navigation system has been proven to be a useful tool in identification of liver segmental boundaries or lymph node mapping during surgery[4–6]. Importantly, owing to its metabolism by the liver and excretion through the bile ducts, ICG clearance test is a frequently used tool to measure hepatic reserve or monitor liver function[7,8]. However, similar to all the pharmaceutical agents utilized in clinical work, ICG is associated with several adverse drug reactions (ADRs) that can impact patient safety and treatment outcomes.

With the increasing use of ICG in clinical practice, there is still a lack of extensive real-world data regarding its safety profile. Although ICG has traditionally been considered a relatively safe drug with only anaphylactic or urticarial reactions recorded in the instruction (Figure S1) and clinical trials offer preliminary insights into the safety, these studies are typically carried out under controlled conditions with selected patient populations and high-dose or long-term use of ICG may introduce new risks[3,9,10]. In addition, the safety of ICG-guided treatment rather than the usage of ICG alone were reported in these clinical trials. This gap highlights the importance of post-marketing surveillance and real-world evidence to capture a comprehensive spectrum of potential adverse effects associated with ICG. This may lead to an under-representation of the full range and frequency of ADRs observed in larger, more diverse populations. As new applications emerge, it is necessary to re-evaluate the safety of ICG to ensure that its widespread use does not introduce previously unrecognized clinical risks.

[1]Department of Hepatobiliary and Pancreatic Surgery, General Surgery Center, The First Hospital of Jilin University, Changchun 130021, China. [2]Department of Radiation Oncology, Jilin Provincial Key Laboratory of Radiation Oncology & Therapy, The First Hospital of Jilin University, Changchun 130021, China. [3]Jilin Provincial Key Laboratory of Tooth Development and Bone Remodeling, School and Hospital of Stomatology, Jilin University, Changchun 130021, China. ✉email: jinmeng@jlu.edu.cn

Individuals may experience notable variations in the metabolism, clearance, and tolerance of ICG, particularly those with compromised liver and kidney function. Since ICG is mainly processed by the liver, those with liver diseases may be at greater risk of drug buildup and toxicity. Current data on adverse reactions in these specific groups are inadequate for a thorough risk evaluation. Thus, investigating ICG's adverse effects in various patient populations can better pinpoint high-risk groups and propose effective preventive measures.

To address this issue, the FDA Adverse Event Reporting System (FAERS) serves as a vital resource for post-marketing drug safety surveillance. FAERS is a spontaneous report database containing adverse events (AEs) reports from healthcare professionals, consumers, and pharmaceutical companies, offering valuable insights into the safety of medications in diverse clinical settings[11–13]. Utilizing such a comprehensive database allows for a more detailed analysis of ICG-related AEs, providing a broader understanding of its safety profile beyond the scope of clinical trials.

Accordingly, we used the FAERS database to perform an in-depth analysis of AEs associated with ICG, employing various methods for signal detection to identify and measure these occurrences. The objectives of this study were to ascertain the most frequent and significant AEs linked to ICG, and to provide actionable insights for healthcare professionals to improve patient management and safety monitoring. Based on comprehensive analysis, the study will enhance our understanding of ICG's safety profile and support better-informed decision-making in clinical practice.

Methods

Study design and data source

We conducted this observational, retrospective study using data from the FAERS database. The FAERS database is publicly accessible and collects spontaneous reports of ADRs from healthcare professionals, patients, and pharmaceutical companies. The data used in this study spans from the first quarter (Q1) of 2004 to the fourth quarter (Q4) of 2023, providing nearly two decades of ICG-associated AEs.

Data extraction and descriptive analysis

We retrieved records related to ICG using the search term "Indocyanine Green" and its trade names. Duplicate reports were removed according to the FDA's guidelines to ensure data accuracy. The AEs were categorized according to the Medical Dictionary for Regulatory Activities terminology[14], which is designated for reporting and classification process standardization of ADRs.

Demographic and clinical characteristics of the reports were analyzed, including report year, reported countries, reporter type, age, gender, and outcomes. Serious outcomes were defined as events leading to death, life-threatening circumstances, disability, hospitalization, or other serious conditions.

Signal detection and statistical analysis

To identify significant signals of ADRs, four disproportionality analysis methods were employed: reporting odds ratio (ROR)[15,16], proportional reporting ratio (PRR)[17], Bayesian confidence propagation neural network (BCPNN)[18,19], and multiitem gamma Poisson shrinker (MGPS)[20]. These methods are extensively used to identify potential drug-AE associations in pharmacovigilance.

The ROR method compares the odds of reporting a specific AE for ICG with the odds of reporting the same AE for all other drugs in the database. PRR is calculated by dividing the proportion of AE reports for ICG by the proportion of reports for all other drugs. The strength of associations between ICG and specific AEs is estimated using the BCPNN method based on Bayesian statistics. The MGPS method adjusts for multiple testing and provides a conservative estimate of signal strength.

Positive signals were defined according to the following criteria: a minimum of three reported cases, a lower limit of the 95% confidence interval (CI) for ROR and PRR exceeding one, a chi-square value of four or more, information component (IC) greater than zero, and empirical Bayesian geometric mean (EBGM) greater than two[21]. The results were analyzed using R software (version 4.4.0).

Data presentation

The findings were displayed at both the system organ class (SOC) level and the preferred term (PT) level. The analysis at the SOC level gave a summary of the reported types of AEs, whereas the PT analysis identified specific clinical adverse reactions with significant signals. We employed descriptive statistics to summarize the data and utilized tables and figures to present a thorough analysis of adverse events related to ICG. This approach enhanced our understanding of its safety profile in real-world clinical settings.

Results

Basic Information on adverse reactions

During 2004Q1 to 2023Q4, a total of 62 adverse event reports related to ICG were identified and analyzed from the FAERS database (Fig. 1). Different drug names of ICG and the corresponding adverse reactions frequency were listed in **Table S1**. Among these 62 cases, the top 3 indications and usages of ICG were vitrectomy ($n=7$, 11.29%), angiogram ($n=6$, 9.68%), and imaging procedure ($n=4$, 6.45%) (**Table S2**). The demographic and clinical characteristics of these reports were summarized in Table 1 and Fig. 2. Most of the ICG-associated AEs originated from the United States ($n=24$, 38.71%), followed by India ($n=3$, 4.84%), Germany ($n=2$, 3.23%), and Japan ($n=2$, 3.23%) (Fig. 2B), with the majority submitted between 2016 and 2020 (54.84%) and the peak occurred in year 2017 (Fig. 2A). Females were more frequently affected than males (50.00% vs. 30.65%) in ICG-associated AEs (Fig. 2C), with adults over 60 years comprising a substantial proportion (35.48%; Fig. 2D). Physicians, pharmacists and other health professionals reported most cases (87.10%; Fig. 2E). With respect to

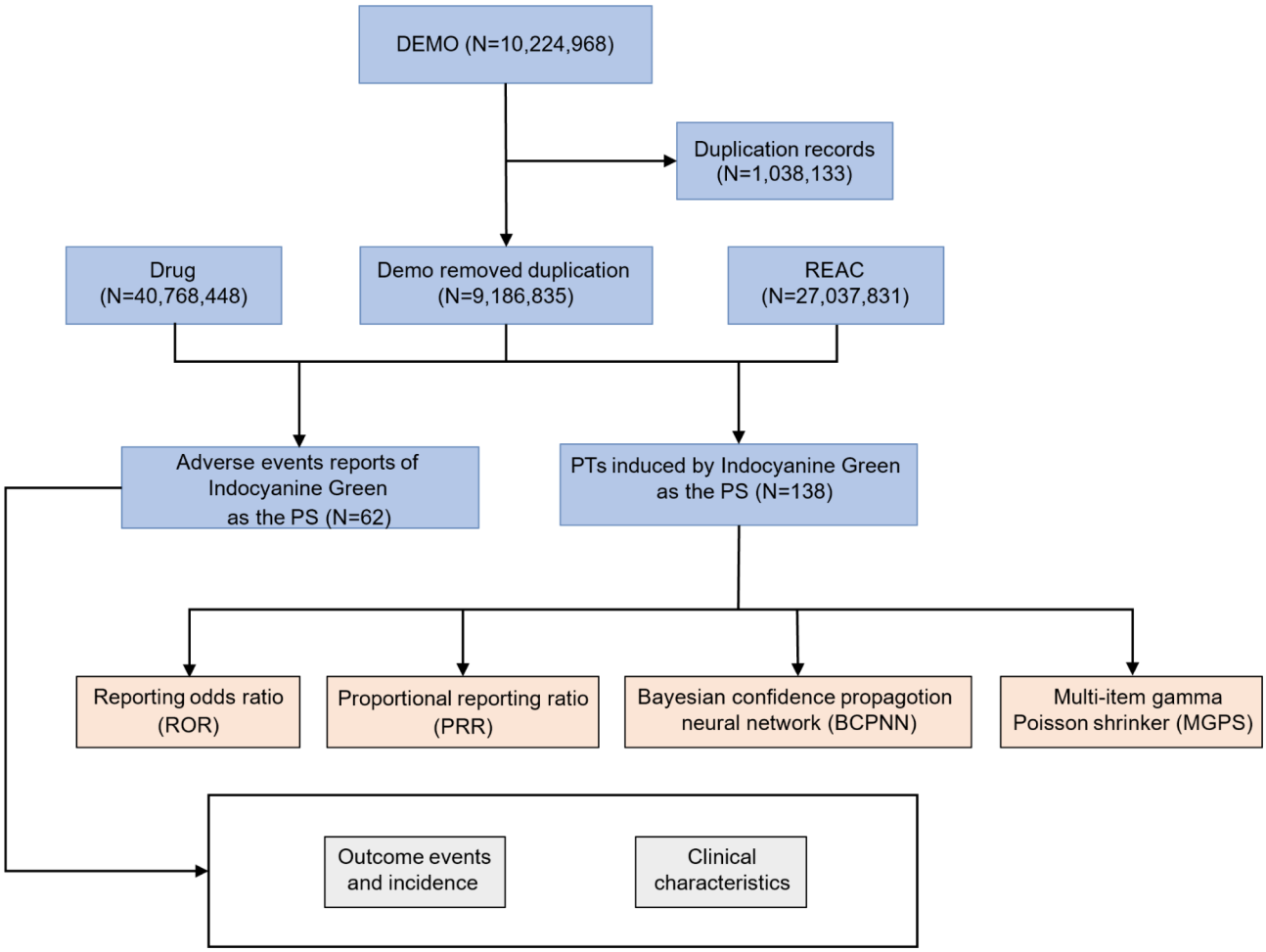

Fig. 1. Flow diagram of the selection process for indocyanine green (ICG)-related adverse events from the FAERS database. The diagram illustrates the steps from initial data extraction, removal of duplicate records, identification of ICG as the primary suspect (PS), to the final selection of adverse events (AEs) and preferred terms (PTs) induced by ICG. The diagram also highlights the application of various signal detection algorithms: reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and multiitem gamma Poisson shrinker (MGPS).

serious outcomes (Fig. 2F), life-threatening events were the most common ($n=10$, 18.87%), followed by events leading to hospitalization ($n=9$, 16.98%), or disability ($n=5$, 9.43%).

Signal detection for ICG-related clinical adverse drug reactions

The signal detection analysis identified significant adverse reactions associated with ICG across various SOCs. Fig. 3 illustrated the frequency of AEs by SOCs, clearly depicting their distribution across various organ systems. Table 2 included a detailed list of the adverse reactions at the SOC level, including the number of case reports, ROR, PRR, chi-square values, IC, and EBGM. ICG was linked to 10 categories, among which immune system disorders ($n=19$; ROR 13.59; PRR 11.86; IC 3.57; EBGM 11.86) and eye disorders ($n=23$; ROR 9.36; PRR 7.96; IC 2.99; EBGM 7.96) were prominently reported, with high ROR and PRR values indicating a strong association with ICG. Additionally, cardiac disorders, and skin and subcutaneous tissue disorders also demonstrated significant signals.

Top clinical adverse reactions

At the PT level, a number of significant clinical adverse reactions were identified. The reported year and quarter and primary ID of each top clinical adverse reaction of ICG were shown in **Table S3**. The top adverse reactions ranked by ROR were listed in Table 3 and Fig. 4. Consistent with the drug specifications, the most frequently reported adverse reactions included anaphylactic shock ($n=5$; ROR 92.10; PRR 88.80; IC 6.47; EBGM 88.76), procedural hypotension ($n=3$; ROR 1397.27; PRR 1366.92; IC 10.41; EBGM 1357.46), and urticaria ($n=4$; ROR 10.88; PRR 10.59; IC 3.41; EBGM 10.59), which were also displayed in the volcano plot (Fig. 5).

Characteristics	Cases ($N=62$)
Reported year	
2007	1 (1.61)
2008	1 (1.61)
2009	3 (4.84)
2010	2 (3.23)
2011	2 (3.23)
2012	6 (9.68)
2013	2 (3.23)
2014	5 (8.06)
2015	1 (1.61)
2016	6 (9.68)
2017	10 (16.13)
2018	8 (12.90)
2019	4 (6.45)
2020	6 (9.68)
2022	1 (1.61)
2023	4 (6.45)
Reporter	
Physician	19 (30.65)
Pharmacist	16 (25.81)
Other health professional	19 (30.65)
Consumer	3 (4.84)
Unknown	5 (8.06)
Reported countries	
The United States	24 (38.71)
India	3 (4.84)
Germany	2 (3.23)
Japan	2 (3.23)
Canada	1 (1.61)
China	1 (1.61)
Italy	1 (1.61)
Korea, South	1 (1.61)
Netherlands	1 (1.61)
Sweden	1 (1.61)
Switzerland	1 (1.61)
Turkey	1 (1.61)
Other countries	23 (37.10)
Sex	
Female	31 (50.00)
Male	19 (30.65)
Unknown	12 (19.35)
Age, years	61.00 (53.50–68.75)
Age group	
< 18	1 (1.61)
18–60	19 (30.65)
≥ 60	22 (35.48)
Unknown	20 (32.26)
Continued	

Characteristics	Cases ($N=62$)
Weight, kg	73.20 (65.09–97.00)
Route of administration	
Intravenous	17 (27.42)
Intravenous bolus	11 (17.74)
Other	34 (54.84)

Table 1. Characteristics of adverse reactions related to indocyanine green in the FAERS database (2004 Q1 to 2023 Q4). Data are n (%) or median (interquartile range). FAERS, FDA Adverse Event Reporting System.

Discussion

Although ICG is a commonly used contrast dye in diagnostic and surgical procedures, there are few reports of adverse reactions associated with ICG alone, most of which focus on ICG-guided surgery-related AEs. Therefore, the present study provides a comprehensive analysis of AEs associated with ICG in a larger and more diverse populations by utilizing real-world data from the FAERS database. To the best of our knowledge, we first investigate and analyze AE signals for ICG using these data, which fills a gap in the pharmacovigilance monitoring of diagnostic dyes. The findings provide useful information on the safety profile of ICG, particularly highlighting significant adverse reactions in the immune, cardiovascular, and skin systems at the SOC level.

Since approved by FDA in 1956, ICG has been playing a significant role in the clinical settings[4,22,23]. The most prominently reported adverse reactions were related to immune system disorders, with anaphylactic shock being the most frequently identified event. The high ROR value suggests a potential association between ICG and this severe adverse reaction; however, further analysis is necessary to confirm this association, taking into account possible confounding factors and biases[24,25]. Anaphylactic shock (a life-threatening allergic reaction) is something that occurs fast and requires immediate medical intervention[26,27]. This finding is consistent with known risks associated with ICG, particularly in patients with allergic or hypersensitivity history[28,29]. Healthcare providers should be aware of and prepared for these reactions, primarily related to ICG diagnostic procedures.

In addition to immune system disorders, cardiovascular disorders such as hypotension also showed a significant association with ICG. Hypotension (low blood pressure) can lead to dizziness, fainting, and even shock if not promptly treated[30]. As a result, blood pressure should be carefully monitored during and after ICG administration, particularly in reference to patients with cardiovascular history[31]. The risk of hypotension is mitigated with proper patient preparation and monitoring.

Another notable category of adverse reactions involved skin and subcutaneous tissue disorders, particularly with reports of urticaria. Although less severe compared to anaphylactic shock or hypotension, skin rashes can still affect patient comfort and treatment adherence[32,33]. Early recognition and prompt management of skin reactions are essential to ensure patient compliance and comfort during routine diagnostic procedures involving ICG.

The analysis also revealed that ICG-related AEs were more frequently reported in female patients, consistent with the broader usage of ICG in specific diagnostic procedures like ophthalmic angiography[34]. The median age of patients experiencing AEs was 61 years, suggesting that middle-aged and older adults may be more susceptible to these reactions. This demographic information can help clinicians identify at-risk populations and tailor monitoring and management strategies accordingly. Interestingly, although ICG is mainly metabolized by the liver, liver disorders were not observed among top clinical adverse reactions in the current study.

Despite providing valuable insights, there are several limitations that need to be acknowledged. First, the FAERS database relies on spontaneous reports, potentially resulting in underreporting and reporting biases. Second, incomplete clinical information in some reports and the lack of reports on the total number of cases that used ICG may hinder a comprehensive understanding of AEs. Third, no causal association between ICG and the reported AEs could be established due to the observational design of this study. Therefore, additional prospective studies are necessary to validate our findings and explore the underlying mechanisms of ICG-related adverse reactions.

Conclusion

This study highlights significant adverse reactions associated with ICG, including 62 reported in total, especially in the immune, cardiovascular, and skin systems. These findings underscore the importance of vigilant monitoring and prevention to ensure the safe use of ICG in clinical practice. Close monitoring, early recognition and prompt management are key to avoid serious AEs, especially among particular population at high risk. Ongoing pharmacovigilance and further research are warranted to fully elucidate potential ICG-related risks and maximize its benefit as a therapeutic or diagnostic agent.

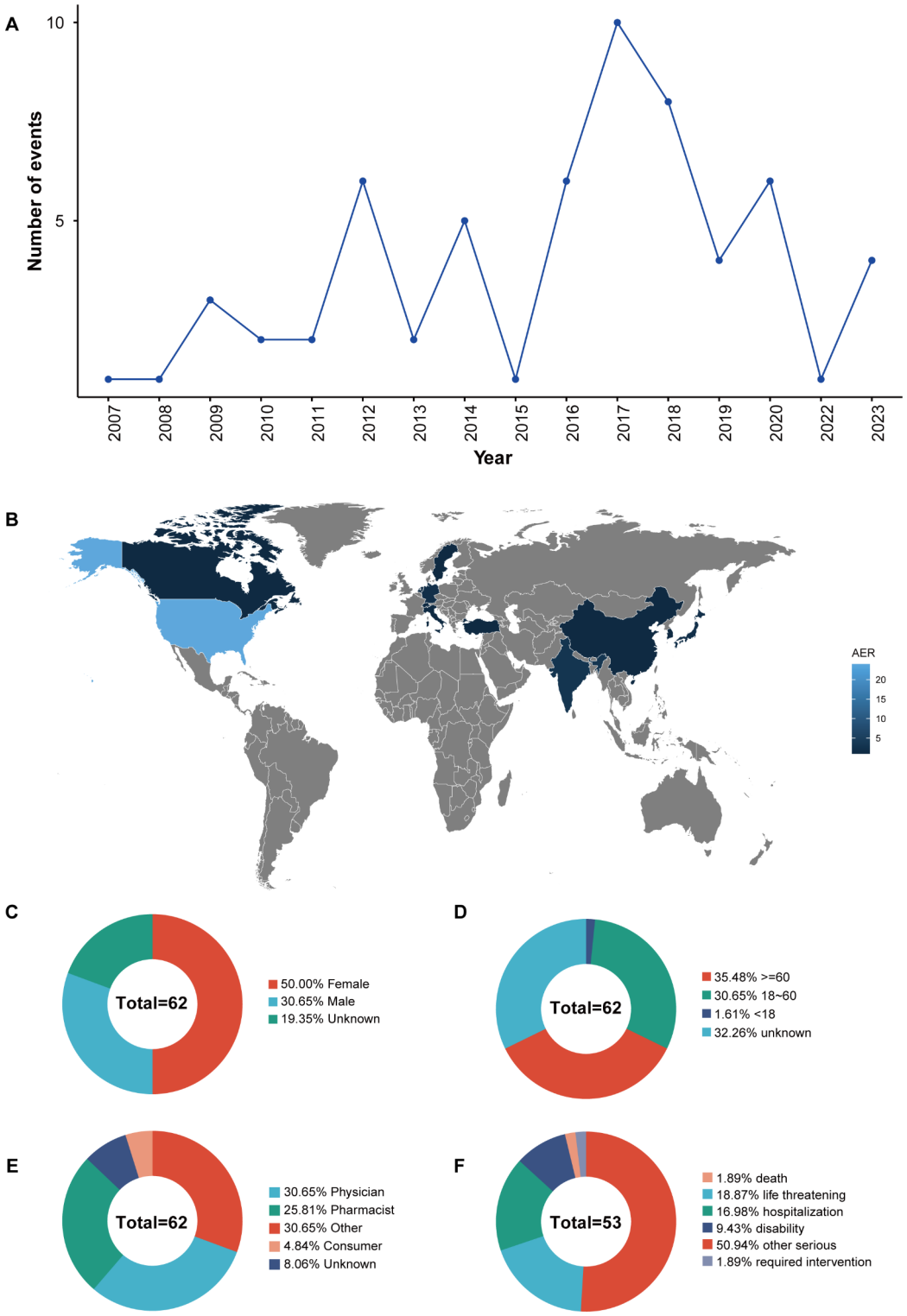

Fig. 2. Basic information and patient characteristics according to the reports. (A) The annual distribution of ICG related AEs reports from 2004 to 2023. (B) Country distribution of AEs for ICG. Darker colors represent a higher number of reports. (C) Gender ratio of male and female in reported events. (D) Age distribution ratio in reported events. (E) Occupational information ratio in reported events. (F) Ratio of outcomes in reported events. Using a proportional area map for visualization, where larger areas indicate a higher number of reporters.

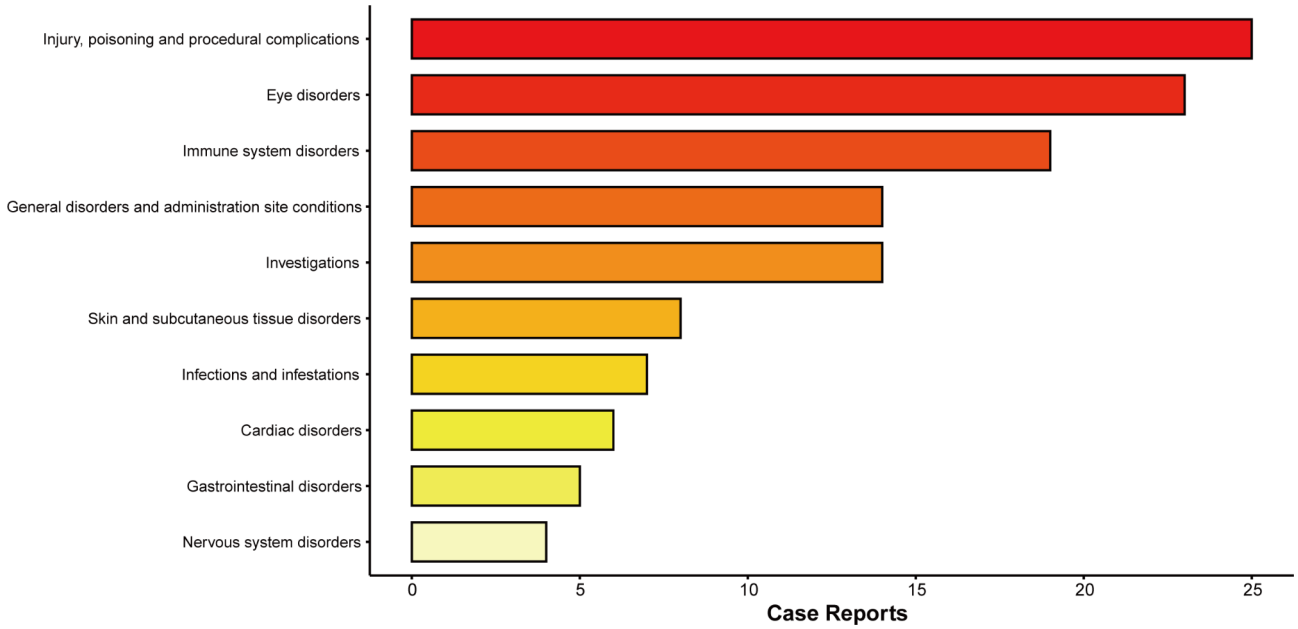

Fig. 3. The distribution of System Organ Classes (SOCs) quantity.

SOC	Case Reports	ROR (95% CI)	PRR (95% CI)	Chisq	IC (IC025)	EBGM (EBGM05)
Immune system disorders	19	13.59 (8.37, 22.06)	11.86 (7.86, 17.9)	191.11	3.57 (2.89)	11.86 (7.91)
Eye disorders	23	9.36 (5.98, 14.64)	7.96 (5.49, 11.55)	143.06	2.99 (2.37)	7.96 (5.48)
Injury, poisoning and procedural complications	25	2.17 (1.41, 3.35)	1.96 (1.38, 2.79)	12.95	0.97 (0.37)	1.96 (1.36)
Investigations	14	1.65 (0.95, 2.87)	1.58 (0.97, 2.58)	3.22	0.66 (−0.10)	1.58 (1.00)
Cardiac disorders	6	1.56 (0.69, 3.55)	1.54 (0.70, 3.37)	1.17	0.62 (−0.47)	1.54 (0.78)
Skin and subcutaneous tissue disorders	8	1.07 (0.53, 2.19)	1.07 (0.55, 2.08)	0.04	0.10 (−0.88)	1.07 (0.59)
Infections and infestations	7	0.90 (0.42, 1.92)	0.90 (0.44, 1.86)	0.08	−0.15 (−1.18)	0.9 (0.48)
General disorders and administration site conditions	14	0.51 (0.29, 0.88)	0.56 (0.34, 0.91)	6.07	−0.85 (−1.62)	0.56 (0.35)
Gastrointestinal disorders	5	0.37 (0.15, 0.91)	0.40 (0.17, 0.95)	5.05	−1.33 (−2.51)	0.40 (0.19)
Nervous system disorders	4	0.30 (0.11, 0.82)	0.32 (0.12, 0.84)	6.20	−1.63 (−2.91)	0.32 (0.14)

Table 2. The adverse reactions of indocyanine green at the SOC level in the FAERS database (2004Q1 to 2023Q4). CI, confidence interval; EBGM, empirical Bayesian geometric mean; IC, information component; PRR, proportional reporting ratio; ROR, reporting odds ratio; SOC, system organ class.

SOC	PT	Case reports	ROR (95% CI)	PRR (95% CI)	Chisq	IC (IC025)	EBGM (EBGM05)
Immune system disorders	Anaphylactic shock	5	92.10 (37.71, 224.96)	88.80 (37.49, 210.35)	434.03	6.47 (5.29)	88.76 (42.04)
Immune system disorders	Anaphylactic reaction	6	53.35 (23.54, 120.93)	51.08 (23.32, 111.88)	294.76	5.67 (4.58)	51.06 (25.75)
Immune system disorders	Drug hypersensitivity	3	5.89 (1.88, 18.49)	5.78 (1.89, 17.67)	11.91	2.53 (1.10)	5.78 (2.22)
Skin and subcutaneous tissue disorders	Urticaria	4	10.88 (4.02, 29.42)	10.59 (4.05, 27.67)	34.85	3.41 (2.12)	10.59 (4.61)
Injury, poisoning and procedural complications	Procedural hypotension	3	1397.27 (443.31, 4404.08)	1366.92 (447.25, 4177.70)	4066.46	10.41 (8.97)	1357.46 (519.46)
Infections and infestations	Endophthalmitis	4	276.28 (102.13, 747.39)	268.30 (102.69, 701.00)	1063.87	8.07 (6.78)	267.93 (116.52)
Eye disorders	Visual acuity reduced	3	36.25 (11.54, 113.82)	35.48 (11.61, 108.44)	100.58	5.15 (3.71)	35.48 (13.62)
Cardiac disorders	Cardiac arrest	3	14.85 (4.73, 46.63)	14.55 (4.76, 44.47)	37.91	3.86 (2.43)	14.55 (5.59)

Table 3. The clinical adverse reactions of indocyanine green ranked by ROR at the PT level in the FAERS database (2004Q1 to 2023Q4). PT, preferred term.

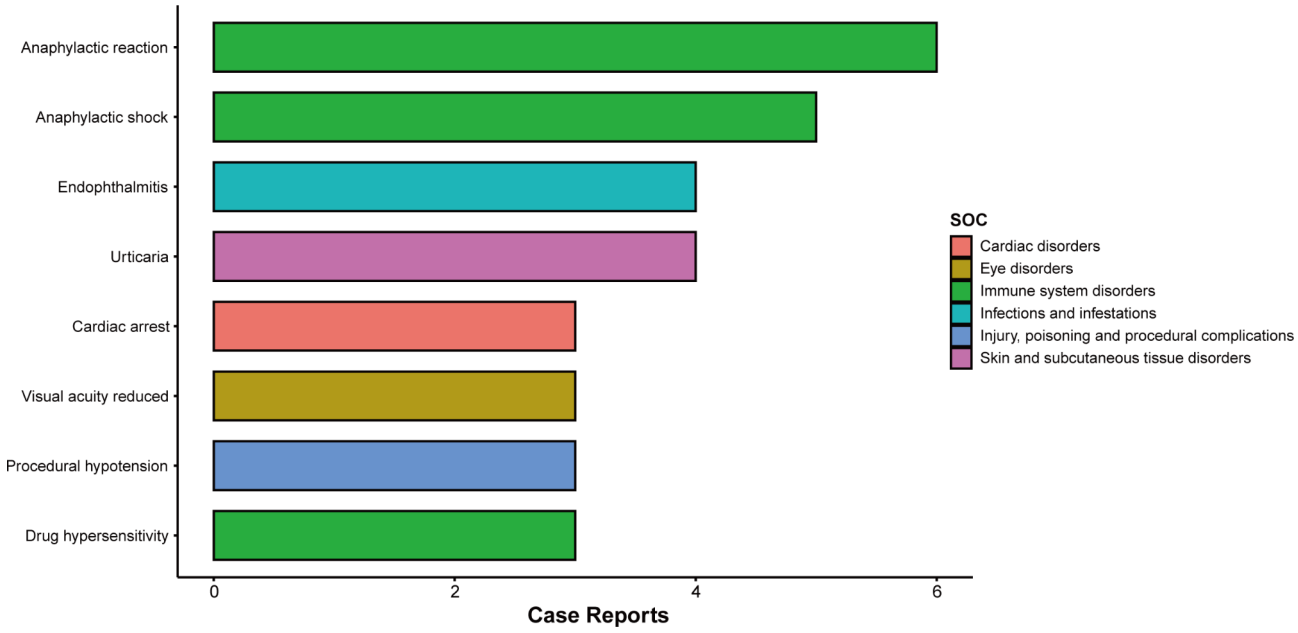

Fig. 4. The top 8 PTs and their affiliated SOCs.

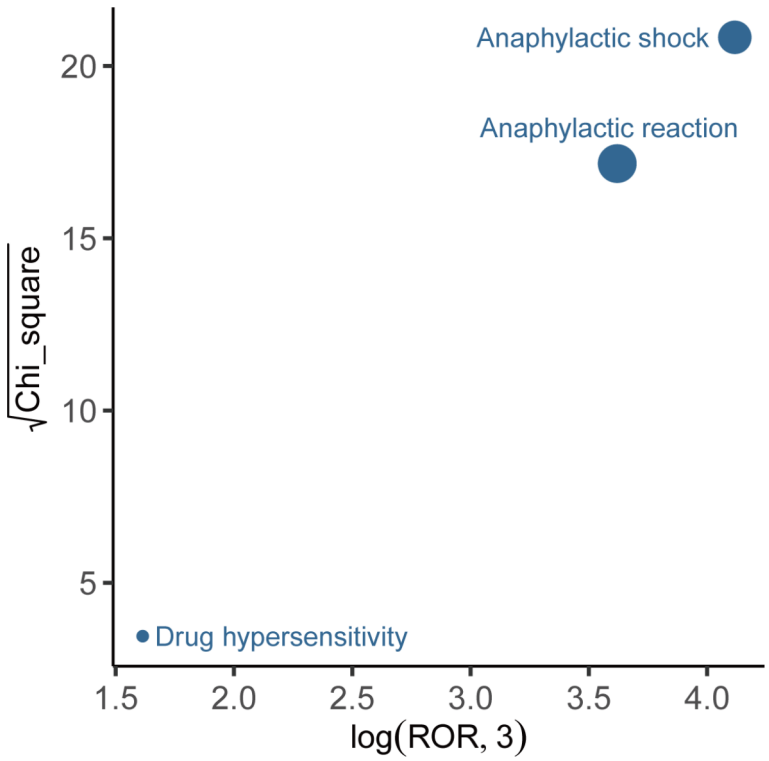

Fig. 5. Risk signal volcano plot for ICG. The horizontal coordinate shows the log2 ROR value and the vertical coordinate indicates the chi-square value.

Data availability

The FAERS database, utilized for this research, is publicly accessible through the FDA's official website. The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Received: 3 September 2024; Accepted: 29 November 2024

Published online: 03 December 2024

References

1. Egloff-Juras, C., Bezdetnaya, L., Dolivet, G. & Lassalle, H. P. NIR fluorescence-guided tumor surgery: new strategies for the use of indocyanine green. *Int. J. Nanomed.* **14**, 7823–7838. https://doi.org/10.2147/IJN.S207486 (2019).
2. Vahrmeijer, A. L., Hutteman, M., van der Vorst, J. R., van de Velde, C. J. & Frangioni, J. V. Image-guided cancer surgery using near-infrared fluorescence. *Nat. Rev. Clin. Oncol.* **10**, 507–518. https://doi.org/10.1038/nrclinonc.2013.123 (2013).
3. Chen, Q. Y. et al. Safety and Efficacy of Indocyanine Green Tracer-guided lymph node dissection during laparoscopic radical gastrectomy in patients with gastric Cancer: a Randomized Clinical Trial. *JAMA Surg.* **155**, 300–311. https://doi.org/10.1001/jamasurg.2019.6033 (2020).
4. Huang, Z. N. et al. Assessment of Laparoscopic Indocyanine Green Tracer-guided Lymphadenectomy after Neoadjuvant Chemotherapy for locally advanced gastric Cancer: a Randomized Controlled Trial. *Ann. Surg.* **279**, 923–931. https://doi.org/10.1097/SLA.0000000000006242 (2024).
5. Wakabayashi, T. et al. Indocyanine Green Fluorescence Navigation in Liver surgery: a systematic review on dose and timing of Administration. *Ann. Surg.* **275**, 1025–1034. https://doi.org/10.1097/SLA.0000000000005406 (2022).
6. Wang, X. et al. Consensus guidelines for the use of fluorescence imaging in hepatobiliary surgery. *Ann. Surg.* **274**, 97–106. https://doi.org/10.1097/SLA.0000000000004718 (2021).
7. Singal, A. G. et al. AASLD Practice Guidance on Prevention, diagnosis, and Treatment of Hepatocellular Carcinoma. *Hepatology* **78**, 1922–1965. https://doi.org/10.1097/HEP.0000000000000466 (2023).
8. Schwarz, C. et al. The value of indocyanine green clearance assessment to predict postoperative liver dysfunction in patients undergoing liver resection. *Sci. Rep.* **9**, 8421. https://doi.org/10.1038/s41598-019-44815-x (2019).
9. Chen, Q. Y. et al. Indocyanine green fluorescence imaging-guided versus conventional laparoscopic lymphadenectomy for gastric cancer: long-term outcomes of a phase 3 randomised clinical trial. *Nat. Commun.* **14**, 7413. https://doi.org/10.1038/s41467-023-42712-6 (2023).
10. Zhong, Q. et al. Clinical implications of indocyanine green fluorescence imaging-guided laparoscopic lymphadenectomy for patients with gastric cancer: a cohort study from two randomized, controlled trials using individual patient data. *Int. J. Surg.* **94**, 106120. https://doi.org/10.1016/j.ijsu.2021.106120 (2021).
11. Anand, K., Ensor, J., Trachtenberg, B. & Bernicker, E. H. Osimertinib-Induced cardiotoxicity: a retrospective review of the FDA adverse events reporting System (FAERS). *JACC CardioOncol.* **1**, 172–178. https://doi.org/10.1016/j.jaccao.2019.10.006 (2019).
12. Arcuri, D., Kaouache, M., Lagace, F., Sasseville, D. & Litvinov, I. A case-control pharmacovigilance study of TNF-alpha inhibitors and interleukin inhibitors on tuberculosis, Candida, lymphoma and suicidality using the FAERS database (2014–2020). *J. Am. Acad. Dermatol.* **89**, 619–621. https://doi.org/10.1016/j.jaad.2023.05.041 (2023).
13. Zhou, C. et al. Psychiatric disorders associated with immune checkpoint inhibitors: a pharmacovigilance analysis of the FDA Adverse Event Reporting System (FAERS) database. *EClinicalMedicine* **59**, 101967. https://doi.org/10.1016/j.eclinm.2023.101967 (2023)
14. Brown, E. G. Using MedDRA: implications for risk management. *Drug Saf.* **27**, 591–602. https://doi.org/10.2165/00002018-200427080-00010 (2004).
15. Rothman, K. J., Lanes, S. & Sacks, S. T. The reporting odds ratio and its advantages over the proportional reporting ratio. *Pharmacoepidemiol Drug Saf.* **13**, 519–523. https://doi.org/10.1002/pds.1001 (2004).
16. van Puijenbroek, E. P. et al. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiol Drug Saf.* **11**, 3–10. https://doi.org/10.1002/pds.668 (2002).
17. Evans, S. J., Waller, P. C. & Davis, S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiol Drug Saf.* **10**, 483–486. https://doi.org/10.1002/pds.677 (2001).
18. Bate, A. et al. A bayesian neural network method for adverse drug reaction signal generation. *Eur. J. Clin. Pharmacol.* **54**, 315–321. https://doi.org/10.1007/s002280050466 (1998).
19. Szarfman, A., Machado, S. G. & O'Neill, R. T. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. *Drug Saf.* **25**, 381–392. https://doi.org/10.2165/00002018-200225060-00001 (2002).
20. Almenoff, J. S., LaCroix, K. K., Yuen, N. A., Fram, D. & DuMouchel, W. Comparative performance of two quantitative safety signalling methods: implications for use in a pharmacovigilance department. *Drug Saf.* **29**, 875–887. https://doi.org/10.2165/00002018-200629100-00005 (2006).
21. Kinoshita, S., Hosomi, K., Yokoyama, S. & Takada, M. Time-to-onset analysis of amiodarone-associated thyroid dysfunction. *J. Clin. Pharm. Ther.* **45**, 65–71. https://doi.org/10.1111/jcpt.13024 (2020).
22. Le-Nguyen, A. et al. Indocyanine green fluorescence angiography in pediatric intestinal resections: a first prospective mixed methods clinical trial. *J. Pediatr. Surg.* **58**, 82–88. https://doi.org/10.1016/j.jpedsurg.2022.09.020 (2023).
23. Abdelrahman, H., El-Menyar, A., Peralta, R. & Al-Thani, H. Application of indocyanine green in surgery: a review of current evidence and implementation in trauma patients. *World J. Gastrointest. Surg.* **15**, 757–775. https://doi.org/10.4240/wjgs.v15.i5.757 (2023).
24. Fusaroli, M. et al. The reporting of a Disproportionality Analysis for Drug Safety Signal Detection Using Individual Case Safety Reports in PharmacoVigilance (READUS-PV): Development and Statement. *Drug Saf.* **47**, 575–584. https://doi.org/10.1007/s40264-024-01421-9 (2024).
25. Fusaroli, M. et al. The REporting of a disproportionality analysis for DrUg Safety Signal Detection using individual Case Safety reports in PharmacoVigilance (READUS-PV): explanation and elaboration. *Drug Saf.* **47**, 585–599. https://doi.org/10.1007/s40264-024-01423-7 (2024).
26. de Silva, D. et al. Diagnosing, managing and preventing anaphylaxis: systematic review. *Allergy* **76**, 1493–1506. https://doi.org/10.1111/all.14580 (2021).
27. Muraro, A. et al. EAACI guidelines: Anaphylaxis (2021 update). *Allergy* **77**, 357–377. https://doi.org/10.1111/all.15032 (2022).
28. Kim, M. et al. Anaphylactic shock after Indocyanine Green Video Angiography during cerebrovascular surgery. *World Neurosurg.* **133**, 74–79. https://doi.org/10.1016/j.wneu.2019.09.135 (2020).
29. Keller, N. B., Stapler, S. M., Shanker, B. A. & Cleary, R. K. Anaphylactic shock to Intravenous Indocyanine Green during a robotic right colectomy. *Am. Surg.* **89**, 6407–6409. https://doi.org/10.1177/00031348231206584 (2023).
30. Juraschek, S. P. et al. Orthostatic hypotension, dizziness, neurology outcomes, and death in older adults. *Neurology* **95**, e1941-e1950, (2020). https://doi.org/10.1212/WNL.0000000000010456
31. Bjerregaard, J., Pandia, M. P. & Jaffe, R. A. Occurrence of severe hypotension after indocyanine green injection during the intraoperative period. *Case Rep.* **1**, 26–30. https://doi.org/10.1097/ACC.0b013e3182933c12 (2013).
32. Price, K. N., Grinnell, M., Butler, D. & Shah, A. Art of prevention: practical tips for improving adherence to treatments for older patients in dermatology. *Int. J. Womens Dermatol.* **7**, 478–481. https://doi.org/10.1016/j.ijwd.2021.03.006 (2021).
33. Kvarnstrom, K., Westerholm, A., Airaksinen, M. & Liira, H. Factors contributing to Medication Adherence in patients with a Chronic Condition: a scoping review of qualitative research. *Pharmaceutics* **13**, 1100. https://doi.org/10.3390/pharmaceutics13071100 (2021).
34. Muraleedharan, S. & Tripathy, K. Indocyanine Green (ICG) Angiography. *in StatPearls*. (2024).

Acknowledgements
We would like to thank the FDA for providing access to the FAERS database, which was instrumental in conducting this study.

Author contributions
Conception and design: M Jin and Y Jiao. Acquisition, analysis and interpretation of the data: Y Jiao and M Jin. Drafting of the paper: Y Jiao. Revising the paper critically for intellectual content: M Jin and Y Liu. All authors read and approved the final manuscript.

Funding
This study was supported by the Doctor of excellence program (DEP), The First Hospital of Jilin University (No. JDYY-DEP-2023028); the Youth Development Foundation of the First Hospital of Jilin University (No. JDYY15202401); and the Special Project for Health Talents of Jilin Provincial Department of Finance (No. JLSWSRCZX2021-071).

Declarations

Competing interests
The authors declare no competing interests.

Data sharing statement
The FAERS database, utilized for this research, is publicly accessible through the FDA's official website. The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics statement
No ethical approval is required for studies using publicly available data from FAERS.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-024-81903-z.

Correspondence and requests for materials should be addressed to M.J.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

© The Author(s) 2024