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FAERS-based pharmacovigilance study of sevoflurane-associated adverse events: A 20-year comprehensive analysis

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Abstract: **Background**: Sevoflurane, an ether-derived inhalational anesthetic widely used for general anesthesia, requires comprehensive safety evaluation. **Objectives**: This study aimed to identify sevoflurane-associated adverse events and detect unexpected safety signals using data from the FDA Adverse Event Reporting System (FAERS). **Methods**: We analyzed FAERS data from the first quarter of 2004 through the first quarter of 2024, applying four disproportionality analysis algorithms (ROR, PRR, BCPNN, MGPS) to reports designating sevoflurane as the "primary suspect" drug. **Results**: Among 1,649 reports, we identified 27 significant preferred terms affecting four major organ systems. Notable unexpected safety signals included cardiac arrest, anesthesia awareness, delayed recovery, pulmonary alveolar hemorrhage, anaphylactic shock and seizures. **Conclusion**: These findings provide critical insights into sevoflurane's real-world safety profile, particularly revealing severe yet underrecognized risks that can inform enhanced clinical monitoring and safer anesthetic practice. However, it should be acknowledged that disproportionality analysis is a hypothesis-generating or refinement approach, and further confirmatory studies are warranted to establish causal relationships.

Keywords: Adverse events; FDA adverse event reporting system; Pharmacovigilance; Sevoflurane

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INTRODUCTION

Sevoflurane is a halogenated inhalational anesthetic, first independently synthesized in the late 1960s (Ikeda, 2022). It was introduced for clinical use in Japan in January 1990 and approved by the Food and Drug Administration (FDA) for sale in the United States in June 1995. Sevoflurane is the most widely used inhaled anesthetic worldwide (Ikeda, 2022). Sevoflurane provides hypnosis, analgesia, amnesia and autonomic blockade during surgery (Edgington, 2023). It is primarily administered via inhalation through a mask, endotracheal tube, or laryngeal mask airway (Miller, 2024) and is characterized by a low blood-gas partition coefficient, rapid onset of action, minimal side effects and low irritability (Ghatge, 2003). Although the precise mechanism by which sevoflurane induces and maintains general anesthesia is not fully understood, the anesthetic properties of sevoflurane arise partly from its ability to boost the function of central nervous system inhibitory receptors, such as those for γ-aminobutyric acid (GABA) and glycine.

The frequently reported adverse effects of sevoflurane consist of nausea and vomiting after surgery, along with dizziness and disorientation; in rare cases, it may trigger malignant hyperthermia (Schuster, 2019). Additionally, sevoflurane can suppress respiration (Wang, 2021), leading to reduced tidal volume, increased respiratory rate and elevated arterial carbon dioxide pressure (Hao, 2021). Sevoflurane also carries potential risks of hepatic, renal and neurotoxicity (Stachnik, 2023). While sevoflurane may degrade into Compound A, it is currently believed that Compound A does not pose significant nephrotoxicity in humans (Taylor, 2023). Through an evaluation of the FDA Adverse Event Reporting System (FAERS), Jacob and colleagues investigated sevoflurane-associated nephrogenic diabetes insipidus (Jacob, 2024). Their analysis revealed a significant association, though further studies are needed to confirm this potential adverse effect (Taylor, 2024). Crucially, several severe but underrecognized adverse events (AEs)-including anaphylaxis, cardiac arrest and neurological complications-carry high clinical priority due to their potential for catastrophic outcomes, prolonged hospitalization, or permanent disability, yet lack comprehensive real-world characterization.

This knowledge gap is particularly important because spontaneous reporting systems like FAERS –one of the world's largest and most comprehensive pharmacovigilance databases - play a crucial role in post-marketing drug safety surveillance. As a publicly accessible, voluntary reporting system (Yang, 2024), FAERS provides unique capabilities for identifying rare, delayed onset, or severe AEs that may be undetected in controlled clinical trials (Xu, 2024). A thorough understanding of both the frequency and clinical severity of these events is critical for developing effective risk mitigation strategies. To address this need, our study leverages FAERS data to: (1) conduct a comprehensive evaluation of sevoflurane-associated AEs, with particular emphasis on high-severity and unexpected signals that may significantly impact patient outcomes and (2) investigate potential gender-related differences in AE profiles to improve clinical recognition and promote safer anesthetic practice.

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MATERIALS AND METHODS

Data source

Utilizing FAERS data from 2004Q1 through 2024Q1, we performed a 20-year pharmacovigilance analysis. AE reports were standardized through MedDRA preferred term (PT) categorization for systematic evaluation (Lin, 2024; Wu, 2023). The AE reports contain fundamental details, including the date of the report and the patient's age. gender, reporting date, reporter, indication, patient outcome and reporting country (Xu, 2024). Only reports identifying sevoflurane as the primary suspect (PS) were included in the analysis. The search method involved querying the FAERS database using both the brand name and generic name of sevoflurane. Non-drug-related issues, such as "POST PROCEDURAL COMPLICATION," "OCCUPATIONAL EXPOSURE TO PRODUCT," "BREAST CANCER RECURRENT," "DEVICE ISSUE," "PRODUCT ODOUR ABNORMAL," and "PRODUCT TAMPERING," were excluded from the PTs.

Statistical analysis

Disproportionality analysis serves as a fundamental tool in pharmacovigilance research (Noguchi, 2021). To identify AE signals, we utilized four algorithms: reporting odds ratio (ROR), proportional reporting ratio (PRR), bayesian confidence propagation neural network (BCPNN) and multi-item gamma poisson shrinker (MGPS). ROR helps mitigate potential biases arising from small report numbers, while the PRR demonstrates higher specificity compared to ROR. The BCPNN enables cross-validation of signals and the MGPS excels at detecting signals of rare AEs (Jiang, 2024). By employing these four complementary algorithms in combination, we significantly reduce false positive results while maintaining the ability to detect rare AEs through careful threshold adjustment. The specific calculation methods and positive signal thresholds for each of these algorithms are detailed in Supplementary Table 1. Drug-related AEs were identified by comparing the proportion of specific drug-related AEs to those of all other drugs. Signals meeting the criteria across all four algorithms were regarded as strong signals at the system organ class (SOC) level. At the PT level, we initially screened for PTs with a reported number ≥ 20; only those that met the criteria for all four indicators were considered significant. We defined unexpected signals as significant AEs not listed on the sevoflurane product label (Shi, 2023). Furthermore, higher scores across the four algorithms indicate greater disproportionality, suggesting a stronger association between the drug and the AE (Guo, 2022).

RESULTS

Basic characteristics

Throughout the study period, a total of 21,035,995 sevoflurane-related reports were submitted to the FAERS database. After excluding duplicate cases, 17,785,793 cases were identified where sevoflurane was the PS. A total of 1,649 AEs were associated with sevoflurane (Fig. 1). Table 1 describes the basic clinical characteristics of sevoflurane-related AEs. The proportion of male and female reports was similar, at 29.4% and 30.7% respectively. The age of the reported cases was unclear in half of the reports, followed by the 18-65 age group (24.4%). More than half of the reports were submitted by physicians (55.1%), followed by other healthcare professionals (25.2%). The United States accounted for the largest share of reports (25%) among reporting countries. Among reported outcomes, Other serious medical events predominated (51.9%), with subsequent frequencies observed for Hospitalization-initial or prolonged (18.2%), Disability (10.8%) and Death (10.5%). The most reported years were from 2014 to 2019, with the number of reports gradually decreasing over time.

Signal of system organ class

Table 2 presents the signal strength of sevoflurane at the SOC level. Using the signal criteria across all four calculation methods, four SOCs were identified: respiratory, thoracic and mediastinal disorders (case = 450), cardiac disorders (case = 389), hepatobiliary disorders (case = 172) and product Issues (case = 170). Among these, hepatobiliary disorders had the highest values.

Signal of preferred terms

We conducted a detailed analysis of PT signals, identifying those with ≥ 20 cases meeting the criteria across all four algorithms as significant. This process revealed 27 notable AEs spanning 12 SOCs. The most common PT was hyperthermia malignant (n = 163). AEs mentioned in the label included tachycardia, bradycardia, cardio-respiratory arrest, anaesthetic complication, anaesthetic complication neurological, mental status changes postoperative, heart rate increased, oxygen saturation decreased, blood pressure decreased, apnoea, laryngospasm, acute kidney injury, nephrogenic diabetes insipidus, hyperthermia malignant, bronchospasm, hepatocellular injury and hypotension. We detected several unlabeled significant AEs, such as cardiac arrest, unwanted awareness during anaesthesia, delayed recovery from anaesthesia, electroencephalogram abnormal, pulmonary alveolar haemorrhage, septic shock, anaphylactic shock, anaphylactic reaction, seizure and rhabdomyolysis. Among all AEs, mental status changes postoperative had the highest score, followed by unwanted awareness during anaesthesia (Table 3).

gender difference risk

Figure 2 shows the gender-specific risk signals associated with sevoflurane use. Females were at higher risk than males for five PTs: unwanted awareness during anaesthesia [ROR 2.58 (1.19-5.60)], vomiting [ROR 2.65 (1.17-6.01)], laryngospasm [ROR 4.04 (1.35-12.11)] and somnolence [ROR 3.69 (1.03-13.26)] (Fig. 2).

Table 1: Clinical features of sevoflurane-related complaints from the FAERS database.

Factors	Number of events	Proportion (%)
Gender		
Female	504	30.7
Male	483	29.4
Unknown	656	39.9
Age		
<18	301	18.3
18-65	401	24.4
65-85	118	7.2
>85	2	0.1
Unknown	821	50
Reporter		
Physician	905	55.1
Other health-professional	414	25.2
Pharmacist	102	6.2
Health Professional	91	5.5
Unknown	71	4.3
Reported countries		
United States	411	25
Country not specified	229	13.9
France	180	10.9
Switzerland	60	3.7
Canada	49	3
Outcome		
Other serious medical event	852	51.9
Hospitalization - initial or prolonged	299	18.2
Life-threatening	178	10.8
Death	172	10.5
Unknown	99	6
Year (Top five)		
2014	294	17.9
2015	229	13.9
2016	174	10.6
2018	140	8.5
2019	126	7.7

Considering the role of gender in various diseases, as well as physiology and pharmacology, this can affect anesthesia management. We conducted gender-stratified analysis using ROR (≥3 cases/gender, 95% CI>1) to identify robust disparities. Higher disproportionality scores across all algorithms indicated stronger drug-AE associations. All analyses used R (4.2.3) with ggplot2 for visualization, ensuring reproducibility. Supplementary Table 1 details algorithm formulas and thresholds, providing transparency for clinical interpretation of results.

Table 2: Sevoflurane-related adverse event signal intensity in the FAERS database at the SOC level

SOC	Case reports	ROR (95% Cl)	PRR (χ2)	EBGM (EBGM05)	IC (IC025)
Respiratory, thoracic and mediastinal disorders	450	2.33 (2.11-2.57)	2.19 (305.31)	2.19 (2.02)	1.13 (-0.54)
Cardiac disorders	389	3.62 (3.27-4.02)	3.39 (672.94)	3.39 (3.11)	1.76 (0.09)
Hepatobiliary disorders	172	4.47 (3.83-5.2)	4.33 (444.38)	4.33 (3.81)	2.11 (0.45)
Product issues	170	2.53 (2.17-2.95)	2.47 (151.14)	2.47 (2.17)	1.3 (-0.36)

Note: SOC, system organ class; ROR, reporting odds ratios; PRR, proportional reporting ratios; χ2, chi-squared; IC, information component; IC025, the lower limit of the 95% CI of the IC; CI, confidence interval; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of the 95% CI of EBGM.

Table 3: Sevoflurane signal strength according to FAERS PT level.

System organ class	Preferred term	Case reports	ROR (95% Cl)	PRR (χ2)	EBGM (EBGM05)	IC (IC025)
Cardiac disorders	Tachycardia	96	15.63 (12.77-19.14)	15.31 (1,284.39)	15.29 (12.91)	3.93 (2.27)
	Cardiac arrest	58	9.88 (7.62-12.8)	9.76 (456.28)	9.75 (7.85)	3.29 (1.62)
	Bradycardia	39	10.16 (7.41-13.93)	10.08 (318.98)	10.07 (7.74)	3.33 (1.67)
	Cardio-respiratory arrest	23	7.51 (4.99-11.32)	7.48 (129.07)	7.47 (5.3)	2.9 (1.24)
Injury, poisoning and procedural complications	Anaesthetic complication	122	692.82 (575.97-833.37)	673.47 (77,666.2)	638.53 (547.09)	9.32 (7.65)
	Unwanted awareness during anaesthesia	70	3,673.05 (2,809.06-4,802.78)	3,614.13 (195,384.3)	2,792.96 (2,231.59)	11.45 (9.77)
	Anaesthetic complication neurological	66	1,701.37 (1,313.27-2,204.16)	1,675.64 (97,206.05)	1,474.68 (1,187.44)	10.53 (8.86)
	Mental status changes postoperative	33	5,674.94 (3,754.5-8,577.68)	5,632.01 (127,399.39)	3,862.27 (2,733.53)	11.92 (10.23)
	Delayed recovery from anaesthesia	30	481.44 (333.89-694.18)	478.13 (13,749.29)	460.26 (338.86)	8.85 (7.18)
	Oxygen saturation decreased	51	13.66 (10.36-18)	13.51 (590.5)	13.49 (10.71)	3.75 (2.09)
	Heart rate increased	44	6.3 (4.68-8.49)	6.25 (194.31)	6.25 (4.87)	2.64 (0.98)
Investigations	Electroencephalogram abnormal	28	122.62 (84.41-178.13)	121.84 (3,322.87)	120.65 (88.27)	6.91 (5.25)
	Blood pressure decreased	24	5.09 (3.41-7.6)	5.07 (78.43)	5.07 (3.62)	2.34 (0.67)
	Apnoea	50	89.24 (67.46-118.05)	88.23 (4,281.66)	87.6 (69.32)	6.45 (4.79)
Respiratory, thoracic and mediastinal disorders	Bronchospasm	32	31.34 (22.12-44.39)	31.11 (930.54)	31.04 (23.19)	4.96 (3.29)
	Pulmonary alveolar haemorrhage	32	88.65 (62.53-125.67)	88.01 (2,733.25)	87.39 (65.26)	6.45 (4.78)
	Laryngospasm	20	103.95 (66.87-161.58)	103.48 (2,012.9)	102.62 (70.95)	6.68 (5.01)
General disorders and administration site conditions	Hyperthermia malignant	163	1,854.42 (1,569.12-2,191.58)	1,785.16 (253,792.02)	1,558.84 (1,355.49)	10.61 (8.94)
Hepatobiliary disorders	Hepatocellular injury	26	20.89 (14.2-30.73)	20.77 (488.7)	20.74 (15.02)	4.37 (2.71)
Immune system disorders	Anaphylactic shock	31	18.12 (12.72-25.81)	18 (497.18)	17.97 (13.37)	4.17 (2.5)
	Anaphylactic reaction	22	6.06 (3.99-9.21)	6.03 (92.43)	6.03 (4.25)	2.59 (0.93)
Infections and infestations	Septic shock	22	7.49 (4.93-11.39)	7.46 (123)	7.45 (5.25)	2.9 (1.23)
Musculoskeletal and connective tissue disorders	Rhabdomyolysis	31	10.71 (7.52-15.25)	10.64 (270.76)	10.63 (7.91)	3.41 (1.74)
Nervous system disorders	Seizure	40	3.28 (2.4-4.48)	3.26 (62.9)	3.26 (2.51)	1.71 (0.04)
Renal and urinary disorders	Acute kidney injury	50	3.63 (2.75-4.8)	3.6 (94.1)	3.6 (2.85)	1.85 (0.18)
	Nephrogenic diabetes insipidus	26	323.34 (218.81-477.81)	321.42 (8,093.39)	313.25 (225.93)	8.29 (6.62)
Vascular disorders	Hypotension	86	6.15 (4.97-7.62)	6.05 (363.59)	6.05 (5.06)	2.6 (0.93)

Note: ROR, reporting odds ratios; χ2, chi-squared; PRR, proportional reporting ratios; IC, information component; IC025, the lower limit of the 95% CI of the IC; EBGM, empirical Bayesian geometric mean; CI, confidence interval; EBGM05, the lower limit of the 95% CI of EBGM.

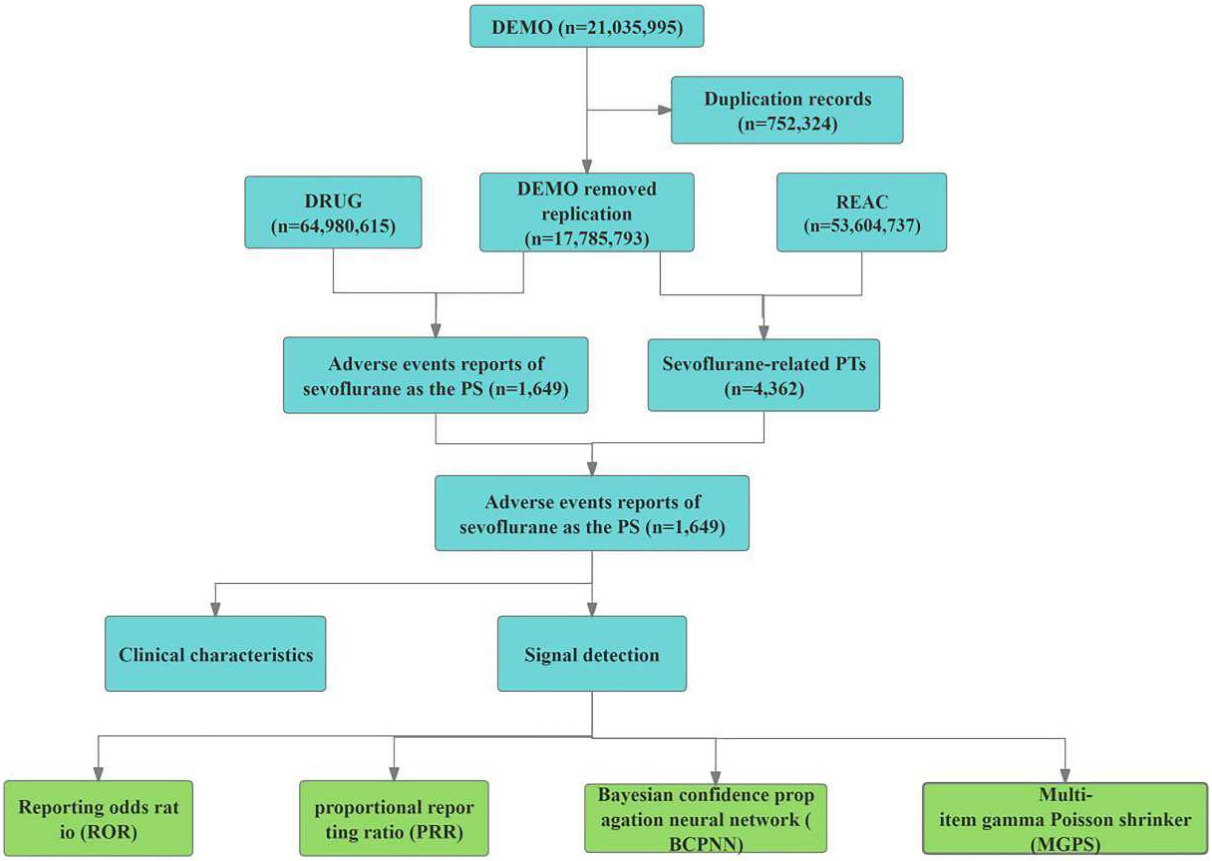

Fig. 1: The flowchart of identifying sevoflurane AEs in FAERS database. Abbreviations: FAERS, United States Food and Drug Administration Adverse Event Reporting System; DEMO, demographic and administrative information file; DRUG, drug information file; REAC, adverse events file; PS, Primary Suspect.

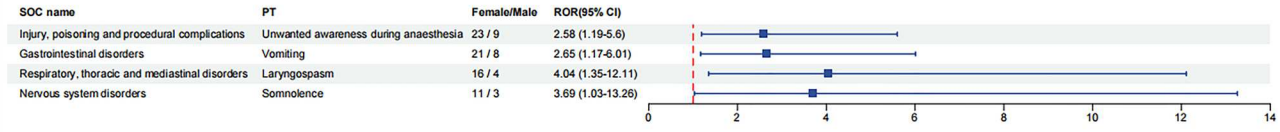

Fig. 2: Analysis of gender-differentiated risk signals in sevoflurane. PT, preferred term; SOC, system organ class; Reporting odds ratios (ROR) with 95% CI for all positive gender-related adverse drug events; CI, confidence intervals. lower limit of 95% CI>1.

DISCUSSION

Our 20-year FAERS analysis provides comprehensive safety insights into sevoflurane use, advancing previous pharmacovigilance studies through three key contributions: (1) extended temporal trend analysis, (2) multi-algorithm signal detection (ROR, PRR, BCPNN, MGPS) and (3) gender-specific risk characterization. Unlike prior studies focusing on specific AEs (Jacob, 2021) or pediatric populations (Yang, 2025), our systematic evaluation across all System Organ Classes offers clinicians a more complete safety reference.

Our study revealed no significant gender differences in the overall AE signals associated with sevoflurane. This observation suggests that the safety profile of sevoflurane is generally consistent across male and female patients. Physicians and other medical experts submitted the majority of the reports, which aligns with sevoflurane's widespread use in clinical settings where such professionals are the primary administrators of anesthesia. Notably, the most frequently reported outcomes were categorized as "Hospitalization-initial or prolonged" and "Other serious medical events". These findings underscore the seriousness of sevoflurane-related AEs, which often necessitate significant medical intervention. This

highlights the importance of heightened vigilance and comprehensive monitoring during its use in anesthesia. Interestingly, the highest number of reports occurred between 2014 and 2019, followed by a declining trend. While this decrease could reflect improved safety practices or reporting fatigue, it underscores the need for continuous and consistent reporting to better understand the long-term safety profile of sevoflurane.

In our study, 163 cases of MH were reported, highlighting it as a critical issue associated with the use of sevoflurane. MH is a relatively rare familial genetic muscle disorder that can be triggered by sevoflurane, leading to clinical symptoms of MH, including muscle rigidity, hyperthermia, elevated end-tidal CO2 concentration and tachycardia (Min, 2021). While the incidence rate is unclear, the mortality rate is notably high (Aires, 2023). Dantrolene is the specific treatment for MH and rapid diagnosis and treatment are crucial for ensuring a positive prognosis in MH patients (Glahn, 2020). Current guidelines recommend immediate access to dantrolene and continuous capnography monitoring when using triggering agents like sevoflurane (Glahn, 2020). Our findings reinforce the necessity for: preoperative MH susceptibility screening using the Clinical Grading Scale and mandatory MH simulation training for anesthesia teams.

Among the 1,649 sevoflurane-related AEs identified, the emergence of unexpected signals, particularly those not listed on the product label, is noteworthy. Our study identified 58 cases of cardiac arrest as unexpected adverse events associated with sevoflurane. While previous studies have established sevoflurane's dose-dependent hypotensive effects through decreased systemic vascular resistance (Eis, 2022), our real-world data specifically highlight cardiac arrest as a potentially underrecognized severe outcome of these hemodynamic changes. The arrhythmogenic potential noted in our cases further supports existing concerns about sevoflurane's myocardial sensitization (Nasiri-Valikboni, 2024), though our data suggest these effects may be more clinically significant than previously appreciated. These results emphasize the need for careful hemodynamic monitoring during sevoflurane anesthesia, particularly in high-risk patients. Our analysis identified 40 cases of seizures associated with sevoflurane, supporting previous observations that high alveolar concentrations may lower seizure threshold (Zheng, 2021). While the exact mechanisms remain unclear, these events may relate to sevoflurane's dual effects on neural circuits (Liang, 2023). Chang et al. found a significant association between general anesthesia and the one-year incidence of postoperative seizures in individuals aged 20-39 (Chang, 2018). Abnormal electroencephalograms may be associated with the rate of induction. Therefore, strengthening EEG monitoring and selecting propofol as a substitute during long-term anesthesia in epilepsy patients are considered (Tatum, 2018; Liu, 2024). Although rare, allergic reactions to volatile anesthetics have been reported (Simonini, 2018) and prompt diagnosis and appropriate treatment are necessary if an allergic reaction occurs. Rhabdomyolysis is one of the hallmarks of MH and we speculate it may be related to MH. These results draw attention to sevoflurane's possible hazards, which may go unnoticed in therapeutic settings.

The gender difference analysis reveals that females have a higher risk of certain AEs, including unwanted awareness during anesthesia, vomiting and laryngospasm. The higher awareness risk in females consistent with Braithwaite et al.'s 2021 findings (Braithwaite, 2023). Possible explanations include pharmacodynamic and pharmacokinetic differences between genders (Madla, 2021; Mauvais-Jarvis, 2021), as well as the potential modulatory role of sex hormones (Kurdi, 2018), with females potentially requiring higher doses than males to achieve the same effective concentration (Braithwaite, 2023). postoperative nausea and vomiting's most reliable independent predictors include female gender and the duration of volatile anesthetic anesthesia (Apfel, 2012), which aligns with our findings that females have a higher risk of vomiting following sevoflurane use. Laryngospasm, a physiological exaggeration of the protective glottic closure reflex (OpenAnesthesia, 2024), may be triggered by anesthetic, patient and surgical factors (Gavel, 2012). Based on these findings, we recommend the following targeted measures for female patients: moderately increase sevoflurane MAC by 0.1-0.2 with routine EEG monitoring; implement enhanced antiemetic prophylaxis; maintain adequate anesthetic depth before extubation with consideration of prophylactic lidocaine; emphasize preoperative evaluation of menstrual cycle status; and ensure emergency preparedness. These evidence-based recommendations, derived from our gender-difference findings and clinical evidence, aim to mitigate anesthesia risks specific to female patients, though implementation should be tailored to individual patient characteristics and institutional protocols. However, as our study included only limited cases, future research should focus on validating these approaches through multicenter randomized trials and further personalizing anesthetic management strategies.

While our study provides important insights into sevoflurane's safety profile, several limitations should be acknowledged: (1) the FAERS database depends on voluntary AE reporting from several sources, which could introduce bias and result in problems including incomplete, misreported, delayed, or underreported reporting; (2) the absence of dosage data and concomitant medication information prevents assessment of dose-response relationships or drug-drug interactions that may modify AE risks; (3) while our multi-method disproportionality analysis enhances signal reliability, the observed

associations require confirmation through controlled studies to establish causality, as confounding by indication or comorbidities cannot be excluded; and (4) the gender differences observed, while biologically plausible, require validation in prospectively collected datasets. These limitations highlight the need for complementary studies using anesthesia registries with detailed perioperative documentation to confirm these findings.

CONCLUSION

This large-scale pharmacovigilance study identifies critical safety signals associated with sevoflurane, including previously unlabeled significant AEs and gender-specific risks. For clinicians, these findings underscore the need for: gender-specific preoperative risk assessment and preparedness to manage potential complications. The unexpected signals highlight important knowledge gaps requiring further clinical validation through controlled studies and multicenter collaborations. Regulatory agencies should evaluate whether current safety labeling adequately reflects these real-world risks. These evidence-based recommendations can optimize sevoflurane's risk-benefit profile in clinical practice.

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Authors' contributions
JC: Writing-original draft, Software, Methodology. ZW: Writing-original draft, Methodology, Formal analysis. SM: Writing-review & editing, Data curation, Conceptualization.

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Data availability statement
The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical approval
Our data is sourced from the publicly accessible FAERS database, which does not contain any patient personal information; therefore, ethical approval is not required. This study was performed in adherence with the READUS-PV guidelines. See supplementary file for the READUS-PV checklist.

Conflict of interest
The authors declare no conflict of interests.

Supplementary data
https://www.pjps.pk/uploads/2026/07/SUP1784372012.pdf

REFERENCES

Aires CCG, de Souza RRL, Amorim JA, Santos FG, Diniz DA, Carneiro SCAS and Vasconcellos RJH (2023). Malignant hyperthermia in maxillofacial surgery: Literature review supported by case presentation. *Spec. Care Dentist.,* **43**(1): 99-108.

Apfel CC, Heidrich FM, Jukar-Rao S, Jalota L, Hornuss C, Whelan RP, Zhang K and Cakmakkaya OS (2012). Evidence-based analysis of risk factors for postoperative nausea and vomiting. *Br. J. Anaesth.,* **109**(5): 742-753.

Braithwaite HE, Payne T, Duce N, Lim J, McCulloch T, Loadsman J, Leslie K, Webster AC, Gaskell A and Sanders RD (2023). Impact of female sex on anaesthetic awareness, depth and emergence: A systematic review and meta-analysis. *Br. J. Anaesth.,* **131**(3): 510-522.

Chang HC, Liao CC, Chang CC, Huang SY, Yeh CC, Hu CJ, Cherng YG and Chen TL (2018). Risk of epilepsy in surgical patients undergoing general or neuraxial anaesthesia. *Anaesthesia*, **73**(3): 323-331.

Edgington TL, Muco E and Maani CV (2024). Sevoflurane. 2023 Jun 5. *In*: StatPearls [Internet]. Treasure Island (FL): *StatPearls Publishing*; 2024 Jan.

Eis S, Kramer J. Anesthesia inhalation agents and their cardiovascular effects. Updated 2022 Jun 4. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK541090/.

Gavel G and Walker R (2012). Extubation guidelines: Management of laryngospasm. *Anaesthesia*, **67**(8): 920-922.

Ghatge S, Lee J and Smith I (2003). Sevoflurane: An ideal agent for adult day-case anesthesia?. *Acta Anaesthesiologica Scand.*, **47**(8): 917-931.

Glahn KPE, Bendixen D, Girard T, Hopkins PM, Johannsen S, Rüffert H, Snoeck MM and Urwyler A (2020). European malignant hyperthermia group availability of dantrolene for the management of malignant hyperthermia crises: European malignant hyperthermia group guidelines. *Br. J. Anaesth.*, **125**(2): 133-140.

Guo M, Shu Y, Chen G, Li J and Li F (2022). A real-world pharmacovigilance study of FDA adverse event reporting system (FAERS) events for niraparib. *Sci. Rep.*, **12**(1): 20601.

Hao X, Ou M, Li Y and Zhou C (2021). Volatile anesthetics maintain tidal volume and minute ventilation to a greater degree than propofol under spontaneous respiration. *BMC Anesthesiol.*, **21**(1): 238.

Ikeda S and Makino H (2022). A round trip: The Japanese contribution to the development of sevoflurane. *Anesth. Analg.*, **134**(2): 432-439.

Jacob AT, Kumar AH, Halivana G, Lukose L, Nair G and Subeesh V (2024). Bioinformatics-guided disproportionality analysis of sevoflurane-induced nephrogenic diabetes insipidus using the FDA adverse event reporting system database. *Br. J. Clin.*

Pharmacol., **90**(8): 1804-1810.

Jiang Y, Zhou L, Shen Y, Zhou Q, Ji Y and Zhu H (2024). Safety assessment of brexpiprazole: Real-world adverse event analysis from the FAERS database. *J. Affect Disord.*, **346**: 223-229.

Kurdi MS and Ramaswamy AH (2018). Does the phase of the menstrual cycle really matter to anaesthesia? *Indian J. Anaesth.*, **62**(5): 330-336.

Liang X, Jiang M, Xu H, Tang T, Shi X, Dong Y, Xiao L, Xie Y, Fang F and Cang J (2023). Maternal sevoflurane exposure increases the epilepsy susceptibility of adolescent offspring by interrupting interneuron development. *BMC Med.*, **21**(1): 510.

Lin J, Chen X, Luo M, Zhuo Q, Zhang H, Chen N, Zhuo Y and Han Y (2024). Safety of tildrakizumab: A disproportionality analysis based on the FDA adverse event reporting system (FAERS) database from 2018-2023. *Front. Pharmacol.*, **15**: 1420478.

Liu X, Jiang T, Xu L, Zhang W and Gao F (2024). Efficacy of propofol and midazolam combination in managing refractory epileptic encephalopathy with spike-wave activation in sleep. *Epilepsy. Behav. Rep.*, **29**: 100732.

Madla CM, Gavins FKH, Merchant HA, Orlu M, Murdan S and Basit AW (2021). Let's talk about sex: Differences in drug therapy in males and females. *Adv. Drug Deliv. Rev.*, **175**: 113804.

Mauvais-Jarvis F, Berthold HK, Campesi I, Carrero JJ, Dakal S, Franconi F, Gouni-Berthold I, Heiman ML, Kautzky-Willer A, Klein SL, Murphy A, Regitz-Zagrosek V, Reue K and Rubin JB (2021). Sex- and gender-based pharmacological response to drugs. *Pharmacol. Rev.*, **73**(2): 730-762.

Miller AL, Theodore D and Widrich J (2023). Inhalational Anesthetic. May 1. In: StatPearls [Internet]. Treasure Island (FL): *StatPearls Publishing*; 2024 Jan.

Min JY, Hong SH, Kim SJ and Chung MY (2021). Delayed-onset malignant hyperthermia in the postanesthetic care unit: A case report. *J. Int. Med. Res.*, **49**(9): 3000605211044201.

Nasiri-Valikboni A, Rashid M, Azimi A, Zarei H and Yousefifard M (2024). Protective effect of sevoflurane on myocardial ischemia-reperfusion injury: A systematic review and meta-analysis. *Int. J. Surg.*, **110**(11): 7311-7330.

Noguchi Y, Tachi T and Teramachi H (2021). Detection algorithms and attentive points of safety signal using spontaneous reporting systems as a clinical data source. *Brief. Bioinform.*, **22**(6): bbab347.

OpenAnesthesia.Laryngospasm. https://www.openanesthesia.org/keywords/laryngospasm/. Accessed July 8 2024.

Schuster F and Johannsen S (2019). Maligne hyperthermie: Pharmakologische therapie - update 2019 Pharmacological Treatment of Malignant Hyperthermia: Update 2019. *Anasthesiol. Intensivmed. Notfallmed. Schmerzther.*, **54**(9): 549-558. German.

Shi X, Cheng Q, Zhao YZ, Zou SP and Sun MH (2023). A real-world pharmacovigilance study of abaloparatide based on the FDA Adverse Event Reporting System (FAERS). *Osteoporos Int.*, **34**(12): 2047-2058.

Simonini A, Brogi E, Gily B, Tosca M, Barbieri C, Antonini F and Del Zotto G (2018). Anaphylactic shock during pediatric anesthesia: An unexpected reaction to sevoflurane. *Front. Pediatr.*, **6**: 236.

Tatum WO, Rubboli G, Kaplan PW, Mirsatari SM, Radhakrishnan K, Gloss D, Caboclo LO, Drislane FW, Koutroumanidis M, Schomer DL, Kasteleijn-Nolst Trenite D, Cook M and Beniczky S (2018). Clinical utility of EEG in diagnosing and monitoring epilepsy in adults. *Clin. Neurophysiol.*, **129**(5): 1056-1082.

Taylor B, Scott TE, Shaw J and Chockalingam N (2023). Renal safety of critical care sedation with sevoflurane: A systematic review and meta-analysis. *J. Anesth.*, **37**(5):794-805.

Wang J, Lei F, Fu YT and Zheng Y (2021). Effect of prenatal cigarette smoke exposure on sevoflurane-induced respiratory suppression in neonatal rats and the protective role of hydrogen sulfide. *Respir. Physiol. Neurobiol.*, **284**: 103582.

Wu XP, Lu XK, Wang ZT, Huang L, Cai RW, Yu HM, Li JY and Xiao J (2023). Post-marketing safety concerns with upadacitinib: A disproportionality analysis of the FDA adverse event reporting system. *Expert Opin. Drug Saf.*, **22**(10): 975-984.

Xu W, Zhu L, Wang J, Shi L, Tang X, Chen Q and Wang L (2024). Safety assessment of Yasmin: Real-world adverse event analysis using the FAERS database. *Eur. J. Obstet. Gynecol. Reprod. Biol.*, **301**: 12-18.

Yang C, Deng B, Wen Q, Guo P, Liu X and Wang C (2025). Safety profiles of sevoflurane in pediatric patients: A real-world pharmacovigilance assessment based on the FAERS database. *Front. Pharmacol.*, **16**: 1548376.

Yang C, Zhao W, Chen H, Yao Y and Zhang J (2024). Cardiac adverse events associated with lacosamide: A disproportionality analysis of the FAERS database. *Sci. Rep.*, **14**(1): 16202.

Zheng J, Du L and Zhang L (2021). Seizure-like movements caused by residual sevoflurane inside the anesthesia machine: A case report. *Medicine (Baltimore)*, **100**(4): e24495.