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European Journal of Medical Research (2025) 30:143
https://doi.org/10.1186/s40001-025-02406-9

European Journal of Medical Research

RESEARCH

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Disproportionality analysis of vibegron-associated adverse events using the FDA adverse event reporting system (FAERS): a real-world pharmacovigilance study

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Abstract

Background Overactive bladder (OAB) syndrome has a significant impact on quality of life, and vibegron has emerged as a therapeutic option. This study aims to evaluate the safety profile of vibegron in a disproportionality analysis by analyzing adverse event (AE) reports from the Food and Drug Administration Adverse Event Reporting System (FAERS) database.

Methods We conducted a retrospective analysis of the FAERS database from January 2021 to September 2023. After duplicate removal and thorough screening, 1137 vibegron-related AE reports were identified. We analyzed these reports for demographic and clinical characteristics, signal detection at the system organ class (SOC) level, and specific AEs.

Results Females comprised a higher percentage (67.72%) of AE reports compared to males. The elderly population (age > 64 years) accounted for 15.84% of the cases. The majority (95.69%) of the reports originated from the USA. Signal detection revealed significant findings across 19 organ systems with notable SOCs, including renal and urinary disorders (ROR = 7.72, 95%CI 6.83–8.72), gastrointestinal disorders (ROR = 1.38, 95%CI 1.21–1.58), and respiratory, thoracic, and mediastinal disorders (ROR = 1.21, 95%CI 1.01–1.45). In addition, several unexpected AEs were identified, such as dry mouth, hot flush, constipation, and increased blood pressure.

Conclusions This study provides comprehensive insights into vibegron's safety profile, revealing both known and unexpected AEs. The findings highlight the need for careful patient selection and monitoring, especially among females and the elderly. The results advocate for ongoing pharmacovigilance and further research to ensure vibegron's safe and effective use in OAB treatment.

Keywords Overactive bladder syndrome, Vibegron, FAERS database, Adverse event, System organ class

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Introduction

Overactive bladder (OAB) syndrome is a prevalent condition affecting millions worldwide, characterized by symptoms, such as urinary urgency, frequency, nocturia, and urge incontinence [1, 2]. According to the International Continence Society, OAB is identified as a condition involving symptoms, such as a sudden, compelling need to urinate (urgency), which may or may not include involuntary leakage of urine (urge incontinence), and is commonly accompanied by frequent urination and the need to urinate at night (nocturia) [3]. This complex of symptoms significantly impacts patients' quality of life, making effective management critical [4]. Epidemiological studies show varying prevalence rates across different populations. In a previous study, the prevalence of OAB was estimated at approximately 16.5%, affecting over 33 million individuals in the United States [5]. The prevalence is higher in women (34%) compared to men (19%) and increases with age [6]. The intricate nature of its etiology, which involves both neurological and urological factors, makes the management of OAB a challenging clinical endeavor.

Pharmacological intervention forms the cornerstone of OAB management, with antimuscarinics being the traditional first-line therapy [7, 8]. However, their usage is often limited by side effects, such as dry mouth and constipation, leading to poor adherence rates [9]. The introduction of β3-adrenoceptor agonists, like vibegron (GEMTESA®), marked a significant advancement in OAB treatment [8]. vibegron, approved by the FDA in 2020, has shown efficacy in improving OAB symptoms with a favorable side-effect profile [10, 11]. According to the available clinical trial data, common adverse effects of vibegron include nasopharyngitis, headache, and upper respiratory tract infection [12]. However, the incidence of these adverse effects was similar to that observed in the placebo group [13]. The advent of vibegron brought new hope to patients who were either intolerant to or not adequately managed by traditional therapies [9, 14]. This transition in therapeutic strategy reflects an evolving understanding of OAB's pathophysiology and a commitment to improving patient care. Nevertheless, the long-term safety profile of vibegron, as with any new medication, requires thorough evaluation in diverse patient populations and real-world settings [15].

Despite these advancements, a thorough understanding of the adverse drug reactions (ADRs) associated with vibegron remains crucial. The Food and Drug Administration Adverse Event Reporting System (FAERS) provides a vast repository of post-market drug safety data, serving as a valuable resource for identifying potential ADRs [16, 17]. The FAERS database's spontaneous reporting nature captures real-world data, offering insights beyond controlled clinical trials. This study aims to excavate the FAERS database to unearth the spectrum of ADRs associated with vibegron in the treatment of OAB.

To the best of our understanding, this study represents the inaugural comprehensive analysis of the ADRs linked with vibegron, utilizing data from the FAERS database. The significance of this analysis lies not only in identifying known ADRs but also in detecting rare or previously unreported events, thus contributing to a more comprehensive pharmacovigilance profile of vibegron. In addition, this study seeks to contextualize the ADRs within the broader epidemiological data of OAB, thereby providing a nuanced understanding of vibegron's safety in diverse populations. The results of this study are expected to offer clinicians, researchers, and patients deeper insights into the safety profile of vibegron, guiding more informed decision-making in OAB management.

Materials and methods

Data source and extraction

This study utilizes the FAERS database (https://www.fda.gov/drugs/drug-approvals-and-databases/fda-adverse-event-reporting-system-faers) as the primary source for data extraction. The FAERS database, a spontaneous reporting system, collects information on adverse events and medication error reports submitted to the FDA. This analysis adheres to the latest Reporting of a Disproportionality Analysis for Drug Safety Signal Detection Using Individual Case Safety Reports in Pharmacovigilance (READUS-PV) guidelines, ensuring compliance in conducting and reporting disproportionality analyses in pharmacovigilance. We extracted all reports listing vibegron as the primary suspect (PS) drug from the first quarter of 2021, coinciding with the FDA's approval of vibegron, until the third quarter of 2023, aligning with the latest FAERS database update available during the study's execution. Data cleaning involved the removal of duplicate and incomplete reports to ensure data quality and reliability.

Study population

The study included all patients with overactive bladder (OAB) reported in the FAERS database who experienced adverse reactions associated with vibegron. Patients were identified using standardized terms from the International Medical Dictionary for Regulatory Activities (MedDRA, version 25.0) relevant to OAB, such as urgency, urinary frequency, nocturia, and urge urinary incontinence. Cases exhibiting these symptoms, with vibegron listed as the primary suspect drug, were included. To ensure accuracy, cases with incomplete or unclear symptom descriptions or those unrelated to

vibegron treatment were excluded. This approach aligns with international pharmacovigilance guidelines, ensuring a robust and representative sample of OAB-related cases. In addition, patient demographics (e.g., age, gender), clinical characteristics, and co-administered medications were recorded to provide a comprehensive context for the observed adverse reactions.

Adverse event coding

The identified adverse events (AEs) were systematically categorized and organized using the system organ class (SOC) and preferred term (PT) as defined in the MedDRA (version 25.0). This approach involves a meticulous analysis, wherein both SOC and PT categories serve as pivotal elements of the present study's data analytical framework. SOC, which categorizes AEs based on the bodily systems affected, and PT, which provides a specific nomenclature for each adverse event, are integral in distilling complex medical data into actionable insights. By adopting this dual-faceted classification scheme, the present study aims to achieve a comprehensive and nuanced understanding of the AEs associated with the pharmaceutical under investigation. This methodology not only enhances the precision of the present study's analysis but also aligns the present study's research with global regulatory standards, ensuring both clarity and consistency in the interpretation and communication of the present study's findings.

Comparator drug selection

The comparator group in the disproportionality analysis included all drugs reported within the FAERS database during the study period (January 2021 to September 2023), excluding vibegron. This approach aligns with standard practices in pharmacovigilance studies, where all other drugs serve as a reference to assess the relative reporting frequency of AEs for the drug of interest. By using the entire FAERS database as a comparator, we ensured a broad and representative reference group, reducing the potential for bias introduced by the selection of specific drug classes or therapeutic areas. The rationale for selecting all other drugs as the comparator is based on the exploratory nature of this study, which aims to identify signals across a wide spectrum of AEs without predefined hypotheses. This method is particularly appropriate for assessing vibegron's safety profile in real-world settings, as it provides a comprehensive benchmark for detecting disproportional reporting.

Statistical analysis

Descriptive statistics were used to analyze the distribution of adverse events among different demographic groups. The reporting odds ratio (ROR) and the proportional reporting ratio (PRR) were calculated to identify disproportionality in the occurrence of specific adverse events associated with vibegron compared to other medications in the database [18–20]. A positive statistical signal was established when case counts exceeded three, the minimal boundary of the 95% confidence interval (CI) of ROR surpassed 1.0, and the Chi-square values of PRP were above 4. A larger ROR indicates a higher incidence of adverse events for vibegron compared to other drugs. The unexpected AE was identified as any significant AE detected that was not previously included in the FDA's drug labeling. All statistical analyses were performed using statistical software (R, version 4.1.2).

Results

Demographic and clinical characteristics of reports

Between January 2021 and September 2023, the FAERS database received 22,576,813 AE reports. Following the removal of duplicates and thorough screening, 1,137 of these reports identified vibegron as the primary suspect drug (Fig. 1). As shown in Table 1, we summarized the detailed characteristics of patients with vibegron-related AEs. Among the reported AEs, a significant disparity was observed in the distribution by gender: females constituted a notably higher percentage, accounting for 67.72%, in stark contrast to males, who comprised only 32.28%. Regarding age distribution, while a substantial 81.53% of the reported cases had unspecified ages, it is noteworthy that a significant

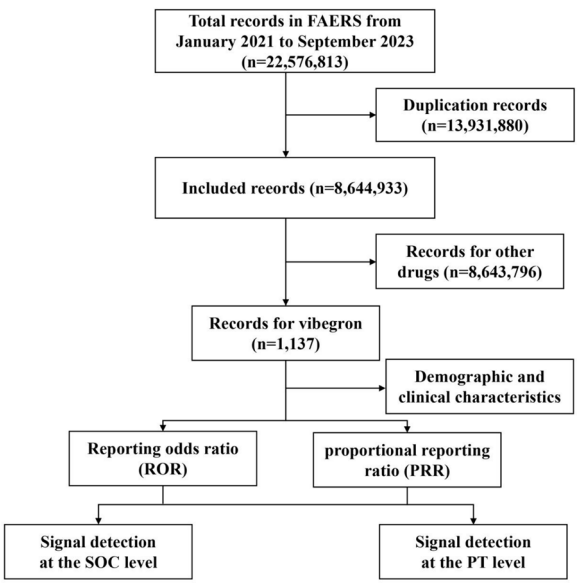

Fig. 1 Flowchart of this research. FAERS = food and drug administration adverse event reporting system; SOC = system organ class; ROR = reporting odds ratio; PRR = proportional reporting ratio; PT = preferred term

Table 1 Characteristics of patients with vibegron-related adverse events

Characteristics	Patient number, n	Case proportion, %
Number of events	1137	
Gender		
Male	367	32.28
Female	770	67.72
Age		
≥ 86	44	3.87
18–64	34	2.99
65–85	132	11.61
Unknown	927	81.53
Occupation of reporter		
Consumer	931	81.88
Health professional	89	7.83
Physician	87	7.65
Pharmacist	24	2.11
Unknown	6	0.53
Reported countries		
Canada	1	0.09
Japan	46	4.05
USA	1088	95.69
Unknown	2	0.17
Reported year		
2023	884	77.75
2022	61	5.36
2021	192	16.89

portion of the AEs occurred in the elderly population, defined as those over 64 years. This demographic accounted for 15.48% of the total cases, amounting to 176 incidents. Regarding the geographic distribution of report sources, a significant majority of the reports, amounting to 95.69%, originate from the United States. In contrast, contributions from other countries are comparatively minimal, with Japan accounting for 4.05%, Canada for a mere 0.09%, and an additional 0.17% stemming from unspecified countries. In terms of the reporters' occupation, a strikingly higher proportion of non-health professionals (81.88%) were observed compared to health professionals (17.59%). In the present study's analysis of the reported years, 2023 emerged as the year with the highest incidence of AEs, accounting for a substantial 77.75% of the total reports. In contrast, the years 2022 and 2021 reported markedly lower percentages of AEs, comprising 5.36% and 16.89% of the total reports, respectively.

Signal detection

Signal values associated with vibegron at the SOC level are detailed in Table 2. Our statistical analysis revealed that vibegron-related adverse events (AEs) were distributed across 19 organ systems. Notably, 4 significant SOCs fully met the established criteria for the computation of positive statistical signals in this study. These included renal and urinary disorders (ROR = 7.72, 95%CI 6.83–8.72), gastrointestinal disorders (ROR = 1.38, 95%CI 1.21–1.58), general disorders and administration site conditions (ROR = 1.35, 95%CI 1.22–1.49), and respiratory, thoracic and mediastinal disorders (ROR = 1.21, 95%CI 1.01–1.45).

At the level of PTs, the present study's analysis found 104 PTs showing significant disproportionality, meeting all four calculation criteria simultaneously. After a thorough manual review, 24 major Preferred Terms (PTs) were identified. During the preprocessing phase, cases unrelated to vibegron or with fewer than three reports were excluded to reduce noise and improve data reliability. This preprocessing step ensures that only meaningful and clinically relevant data are retained for disproportionality analysis. Detailed information is displayed in Table 3. The SOCs covered in AEs listed the infections and infestations, investigations, nervous system disorders, respiratory, thoracic and mediastinal disorders, immune system disorders, skin and subcutaneous tissue disorders, general disorders and administration site conditions, gastrointestinal disorders, cardiac disorders, and vascular disorders. PTs previously reported in clinical AEs include rhinorrhoea (ROR = 14.78, 95%CI 10.68–20.46), urinary tract infection (ROR = 7.36, 95%CI 5.49–9.85), nasal congestion (ROR = 5.24, 95%CI 2.9–9.47), headache (ROR = 3.14, 95%CI 2.46–4.00), and diarrhoea (ROR = 2.8 95%CI 2.19–3.58).

Of particular interest, this study identified several unexpected but important AEs not previously associated with vibegron. These included dry mouth (ROR = 8.23, 95%CI 5.3–12.78), hot flush (ROR = 5.5, 95%CI 3.25–9.31), flushing (ROR = 3.7, 95%CI 1.99–6.89), constipation (ROR = 3.36, 95%CI 2.27–4.99), flatulence (ROR = 3.31, 95%CI 1.48–7.37), blood pressure increased (ROR = 2.76, 95%CI 1.66–4.59), urticaria (ROR = 2.49, 95%CI 1.47–4.22), peripheral swelling (ROR = 2.48, 95%CI 1.56–3.94).

Discussion

Our comprehensive analysis of the FAERS database from January 2021 to September 2023 has provided valuable insights into the safety profile of vibegron, particularly in the treatment of OAB. This study stands out due to its real-world context, offering a more nuanced

Table 2 Signal strength of vibegron-related adverse events at the SOC level

SOC	Patient number, *n*	ROR (95% CI)	PRR (χ^2)
Renal and urinary disorders	300	7.72 (6.83–8.72)	6.80 (1514.17)
Nervous system disorders	167	0.99 (0.84–1.16)	0.99 (0.02)
Injury, poisoning and procedural complications	117	0.43 (0.36–0.52)	0.46 (82.65)
Gastrointestinal disorders	239	1.38 (1.21–1.58)	1.34 (22.65)
Skin and subcutaneous tissue disorders	127	0.94 (0.79–1.13)	0.95 (0.40)
Musculoskeletal and connective tissue disorders	43	0.36 (0.26–0.48)	0.37 (48.77)
Infections and infestations	102	0.83 (0.68–1.01)	0.84 (3.37)
Cardiac disorders	24	0.52 (0.35–0.78)	0.53 (10.32)
Hepatobiliary disorders	6	0.33 (0.15–0.73)	0.33 (8.17)
General disorders and administration site conditions	489	1.35 (1.22–1.49)	1.27 (34.48)
Metabolism and nutrition disorders	13	0.29 (0.17–0.50)	0.29 (22.39)
Respiratory, thoracic and mediastinal disorders	122	1.21 (1.01–1.45)	1.20 (4.12)
Reproductive system and breast disorders	5	0.32 (0.13–0.77)	0.32 (7.21)
Psychiatric disorders	39	0.31(0.23–0.43)	0.32 (57.95)
Vascular disorders	36	0.86 (0.62–1.20)	0.86 (0.79)
Immune system disorders	21	0.79 (0.51–1.21)	0.79 (1.18)
Eye disorders	36	0.85 (0.61–1.19)	0.86 (0.89)
Ear and labyrinth disorders	7	0.74 (0.35–1.55)	0.74 (0.66)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11	0.14 (0.08–0.25)	0.14 (58.63)

SOC = system organ class; ROR = reporting odds ratio; CI = confidence interval; PRR = proportional reporting ratio; χ^2 = chi-squared

understanding of vibegron's safety beyond controlled clinical settings.

Demographic and clinical characteristics

The demographic breakdown of adverse events (AEs) reveals a gender disparity, with females representing a significantly higher percentage (67.72%) compared to males (32.28%). This gender-based difference in AEs could be associated with the notably higher incidence of OAB in females, ranging from 9 to 43%, compared to males, who exhibit a prevalence of 7 to 27% [21, 22]. The elderly demographic represents 15.48% of adverse events, may be attributed to the fact that the prevalence and severity of OAB increase with age [21, 23].

The geographic distribution of reports, predominantly from the USA, reflects not only the usage patterns of vibegron but also the reporting practices. This predominance underscores the importance of understanding cultural and healthcare system differences that may influence drug usage and reporting behaviors [24, 25]. The variation in AE reporting between countries suggests potential differences in patient demographics, healthcare systems, or prescribing practices, which could affect the generalizability of the present study's findings.

Signal detection and AEs

Our signal detection analysis provided a detailed view of the AEs associated with vibegron, with significant findings across 19 organ systems. Notably, renal and urinary disorders exhibited the highest ROR value, suggesting a pronounced risk in this area. This finding is particularly relevant given vibegron's indication for OAB, which inherently involves renal and urinary systems [26, 27].

The significant SOCs, including gastrointestinal and respiratory disorders, align with known pharmacological effects of vibegron but also highlight areas, where vigilance in monitoring is essential [8, 28]. The emergence of unexpected AEs, such as dry mouth, hot flush, and constipation, adds a new dimension to the present study's understanding of vibegron's safety profile [29, 30]. These findings may reflect individual variability in drug response, underlying health conditions, or interactions with other medications.

Moreover, the observed increased blood pressure aligns with evidence reported in phase 3 clinical trials of vibegron, where minor increases in blood pressure were noted among certain subgroups [31, 32]. This finding highlights the importance of monitoring cardiovascular effects in susceptible populations, such as the elderly or those with pre-existing hypertension. Literature suggests that β3-agonists may indirectly influence systemic vascular resistance, although the precise mechanism remains unclear [33, 34].

Furthermore, the high proportion of non-health professional reporters is indicative of a shift towards

Table 3 Signal strength of vibegron-related adverse events at PT level

SOC	PT	Patient number, *n*	ROR (95% CI)	PRR (χ^2)	Whether it is mentioned in the drug label
Infections and infestations	Urinary tract infection	46	7.36 (5.49–9.85)	7.22 (247.18)	Yes
Investigations	Blood pressure increased	15	2.76 (1.66–4.59)	2.75 (16.77)	No
Nervous system disorders	Cerebrovascular accident	9	2.05 (1.06–3.94)	2.05 (4.82)	No
	Headache	67	3.14 (2.46–4.00)	3.07 (94.59)	Yes
Respiratory, thoracic and mediastinal disorders	Cough	18	1.7 (1.07–2.71)	1.7 (5.17)	Yes
	Oropharyngeal pain	8	2.35 (1.17–4.7)	2.34 (6.17)	Yes
	Nasal congestion	11	5.24 (2.9–9.47)	5.22 (37.51)	No
	Rhinorrhoea	37	14.78 (10.68–20.46)	14.55 (466.64)	Yes
Immune system disorders	Hypersensitivity	16	2.33 (1.42–3.8)	2.32 (12)	No
Skin and subcutaneous tissue disorders	Rash	36	2.22 (1.6–3.09)	2.2 (23.78)	No
	Urticaria	14	2.49 (1.47–4.22)	2.48 (12.44)	No
General disorders and administration site conditions	Oedema peripheral	7	2.38 (1.13–4.99)	2.37 (5.57)	No
	Peripheral swelling	18	2.48 (1.56–3.94)	2.47 (15.76)	No
	Feeling hot	7	3.5 (1.66–7.34)	3.49 (12.43)	No
Gastrointestinal disorders	Abdominal pain upper	14	2 (1.18–3.38)	1.99 (6.93)	No
	Abdominal distension	8	2.36 (1.18–4.72)	2.35 (6.22)	Yes
	Dysphagia	7	2.43 (1.16–5.11)	2.43 (5.88)	No
	Diarrhoea	66	2.8 (2.19–3.58)	2.75 (74.05)	Yes
	Flatulence	6	3.31 (1.48–7.37)	3.3 (9.63)	No
	Constipation	25	3.36 (2.27–4.99)	3.33 (40.99)	No
	Dry mouth	20	8.23 (5.3–12.78)	8.16 (125.72)	No
Cardiac disorders	Palpitations	8	2.11 (1.06–4.23)	2.11 (4.68)	No
Vascular disorders	Flushing	10	3.7 (1.99–6.89)	3.69 (19.63)	No
	Hot flush	14	5.5 (3.25–9.31)	5.48 (51.24)	No

SOC = system organ class; PT = preferred term; ROR = reporting odds ratio; CI = confidence interval; PRR = proportional reporting ratio; χ^2 = chi-squared

patient-centered pharmacovigilance. This shift emphasizes the value of patient experiences and perceptions in understanding drug safety, which can sometimes differ from clinical trial outcomes.

Implications for clinical practice and future research

The study's results emphasize the need for individualized treatment approaches, especially considering gender, age, and existing comorbidities. Tailoring vibegron therapy to individual patient profiles could enhance both efficacy and safety [35–37]. Given the high incidence of AEs reported by non-health professionals, there's a need for improved patient education about potential side effects. This approach could lead to more informed patients who are better equipped to report AEs and seek timely medical intervention. The shift in the trend of AEs reported over the years, particularly the spike in 2023, highlights the evolving nature of drug safety profiles. It underscores the importance of ongoing surveillance and reassessment of drug safety in response to changing usage patterns and patient demographics.

The need for longitudinal studies to explore the long-term safety of vibegron, especially in populations like the elderly or those with renal impairment, is apparent [9]. Such studies could provide crucial insights into the risk–benefit profile of vibegron in these sensitive groups. Investigating the mechanisms underlying unexpected AEs, such as dry mouth and hot flushes, may offer valuable insights into vibegron's broader effects beyond its primary pharmacological action [9, 13]. This could potentially lead to the development of strategies to mitigate these effects or the creation of safer therapeutic alternatives. Research exploring patient-reported outcomes, particularly in terms of quality of life and drug tolerance, could provide a more holistic view of vibegron's impact [12, 38]. Understanding the patient's perspective is vital for optimizing treatment strategies and improving overall patient care.

Conclusions

The present study provides a comprehensive overview of vibegron's safety profile in a real-world setting, highlighting both known and unexpected AEs. The demographic and clinical characteristics of the reports, along with the signal detection analysis, offer crucial insights for healthcare providers and patients. Continuous vigilance and patient-centered approaches are essential for maximizing the therapeutic benefits of vibegron while minimizing risks. Future studies should focus on deepening the present study's understanding of the AEs associated with vibegron, especially in diverse patient populations, to ensure safe and effective management of OAB.

Acknowledgements
We would like to thank the participants and investigators of the database we used in this study.

Author contributions
Bangbei Wan, Weiying Lu, Ning Ma and Zhi Zhou designed the study and analyzed the data; Bangbei Wan and Ning Ma revised the images; Bangbei Wan performed the literature search and collected data for the manuscript; Bangbei Wan and Weiying Lu revised the manuscript. All authors have read and approved the final manuscript.

Funding
This work was supported by grants from the Hainan Province Clinical Medical Center (QWYH202175), the Scientific Research Project of Hainan Health Committee (21A200115), the Research and Cultivation Fund of Hainan Medical University (HYPY2020015), the Specific Research Fund of The Innovation Platform for Academicians of Hainan Province (YSPTZX202311), the Natural Science Foundation of Hainan Province (820RC771), and the Key R&D Projects of Hainan Province (ZDYF2022SHFZ074).

Data availability
The data underlying the results presented in the study are available from http://www.fda.gov.

Declarations

Ethics approval and consent to participate
Ethical approval and consent were not required as this study was based on publicly available data.

Competing interests
The authors declare no competing interests.

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Received: 9 January 2024 Accepted: 24 February 2025
Published online: 27 February 2025

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