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Safety profile of faricimab: a multi-source pharmacovigilance analysis using FAERS and JADER

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Abstract

Background Faricimab is a bispecific antibody targeting vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang-2), offering a novel therapeutic approach for ocular diseases. However, its long-term safety profile remains under evaluation. This study analyzes its adverse events (AEs) using the U.S. FDA Adverse Event Reporting System (FAERS) and the Japanese Adverse Drug Event Report (JADER).

Methods AEs from FAERS (2004–2024) and JADER (2004–2024) were analyzed using disproportionality algorithms. Subgroup analyses assessed differences by age and sex. AE onset time was also assessed.

Results Several newly identified adverse events (AEs) were observed, including macular ischemia, keratic precipitates, and optic nerve injury, with strong safety signals detected in both FAERS and JADER. For instance, macular ischemia showed a high association with faricimab use (ROR = 260.46), suggesting a potential risk of retinal circulation impairment. Similarly, keratic precipitates (ROR = 739.65) indicate a notable inflammatory response. All these findings highlight the need for closer monitoring of ocular complications, particularly in high-risk patient groups. The FAERS database mainly reported retinal occlusive vasculitis, ocular vasculitis, and keratic precipitates, while JADER predominantly featured retinal occlusive vasculitis and retinal vascular occlusion. Sex-based differences indicated a higher risk of inflammatory AEs in females (e.g., uveitis and eye inflammation) and a greater incidence of retinal vascular events in males (e.g., retinal vasculitis). Age-related differences showed that older patients (≥65 years) had lower inflammatory AE risks but were more prone to optic nerve damage and retinal atrophy, while younger patients (<65 years) exhibited a higher risk of vitreous hemorrhage and cataracts.

Conclusions This study identified previously unreported safety signals, suggesting the need for potential updates to faricimab's safety labeling. Faricimab's dual-target mechanism presents unique safety concerns. Clinicians should monitor ocular inflammation and vascular complications, particularly in younger males and Asian patients. Further studies using real-world data are needed to validate these findings.

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Keywords Faricimab, Adverse event (AE), FDA adverse event reporting system (FAERS), Japanese adverse drug event report (JADER), Ocular diseases

Introduction

Diabetic macular edema (DME), neovascular age-related macular degeneration (nAMD), and macular edema secondary to retinal vein occlusion (RVO) are among the leading causes of vision loss worldwide, significantly impacting patients' quality of life [1, 2]. These conditions are closely associated with vascular endothelial growth factor (VEGF), which promotes abnormal angiogenesis and increases vascular permeability, leading to retinal edema and macular damage [3]. Consequently, anti-VEGF therapy has become the cornerstone of DME and nAMD treatment, effectively inhibiting pathological vascular proliferation and reducing macular edema [3, 4]. However, prolonged use of conventional anti-VEGF agents may lead to diminished efficacy in some patients due to treatment resistance. Additionally, anti-VEGF therapy has been associated with adverse events (AEs) such as retinal inflammation and increased intraocular pressure, underscoring the need for safer and more effective therapeutic options [5].

Faricimab is an innovative dual-target antibody that inhibits both VEGF and angiopoietin-2 (Ang-2). Ang-2 plays a pivotal role in vascular endothelial stability and inflammatory regulation, with elevated Ang-2 levels contributing to vascular instability and inflammatory responses [6, 7]. Compared to conventional single-target VEGF inhibitors, faricimab's dual mechanism is believed to not only suppress pathological angiogenesis but also enhance vascular wall stability, reduce vascular leakage, and mitigate inflammation, potentially offering superior therapeutic benefits [6, 8]. Large-scale clinical trials, such as the YOSEMITE and RHINE studies, have demonstrated that faricimab effectively manages DME and supports extended dosing intervals in selected patients [9]. However, due to its complex dual-target mechanism, faricimab may be associated with AEs distinct from those observed with traditional anti-VEGF agents, including retinal inflammation, vascular occlusion, and glaucoma [10]. As faricimab's clinical adoption continues to expand, a thorough evaluation of its safety profile has become a critical research priority.

Previous research and knowledge gaps

In recent years, pharmacovigilance database studies have provided preliminary insights into the safety profile of faricimab. For instance, Han's research, using data from the U.S. FDA Adverse Event Reporting System (FAERS) database, identified 121 AE signals associated with faricimab, including some not listed in the official prescribing information, such as retinal hemorrhage, anterior chamber inflammation, and dry eye [11]. Furthermore, Wu's research analyzed FAERS data and reported a potential association between faricimab and an increased risk of glaucoma (ROR = 13.9) [12]. While these studies have generated valuable safety signals, they exhibit several limitations, including a lack of cross-validation with other pharmacovigilance databases, insufficient stratification by patient demographics (e.g., sex and age groups), and an absence of time-dependent analysis of AE occurrence patterns. These limitations highlight the need for a more comprehensive pharmacovigilance study to improve the understanding of faricimab's safety profile and optimize its clinical use.

Study objectives and significance

To address the limitations of previous studies, this study utilizes both the FAERS and the Japanese Adverse Drug Event Report (JADER) pharmacovigilance databases to conduct a comprehensive safety assessment of faricimab [13, 14]. Unlike prior studies, this research employs cross-database validation, comparing AE reports from FAERS and JADER to explore potential geographic and demographic differences in faricimab-associated AEs, thereby identifying possible regional trends and reporting biases. Additionally, this study performs subgroup analyses to compare AE incidence across different sex and age groups, aiming to identify high-risk populations and provide clinicians with personalized pharmacovigilance insights.

Furthermore, this study incorporates drug-induced time analysis to examine the temporal distribution of AEs, investigating short-term versus long-term AE occurrence patterns to optimize clinical monitoring strategies. By analyzing the onset timing of AEs, this study aims to provide a clearer framework for safety monitoring, reducing the risk of severe AEs. Additionally, this study compares faricimab's safety profile with those of other anti-VEGF agents, evaluating whether its dual-target mechanism leads to a distinct AE pattern, ultimately informing therapeutic decision-making for ophthalmic diseases.

The findings of our study will provide clinicians with critical insights into AE risk management and contribute to enhanced drug safety surveillance and personalized treatment strategies. Through an in-depth analysis of AE signals from FAERS and JADER, this study aims to refine the clinical application of faricimab, improve patient safety management, and advance pharmacovigilance research in ophthalmology.

Materials and methods

Data source and collection

This study utilized data from the FAERS and JADER databases, collecting all AE reports related to faricimab from January 1, 2004, to September 30, 2024, for FAERS and from January 1, 2004, to October 31, 2024, for JADER. The data were classified according to the standards of the Medical Dictionary for Regulatory Activities (MedDRA) version 27.0, specifically using System Organ Class (SOC) and Preferred Terms (PT) for the standardized description of AEs. In this classification, SOC identifies the category of AEs, while PT records the specific event names.

During data extraction, we included all reports related to faricimab from both the FAERS and JADER databases. These databases contain multiple tables, including demographic information (DEMO), adverse event information (REAC), patient outcomes (OUTC), drug details (DRUG), therapy duration (THER), reporting source (RPSR), and indications for use (INDI). To ensure comprehensive capture of all relevant reports, we utilized both the generic name and brand name of faricimab in the DRUG table for filtering. After data extraction, we applied the FDA-recommended deduplication strategy to ensure the uniqueness and accuracy of the reports. For records with the same report number (CASE ID) but different report dates (FDA_DT), only the latest report was retained. If both CASE ID and FDA_DT were identical, the entry with the higher primary ID was selected to ensure retention of the most complete information. The deduplication process was implemented using scripts written in R version 4.3.3 to efficiently process large volumes of data, and all deduplicated data were imported into Microsoft Excel for manual review to ensure there were no omissions or errors. A total of 4234 reports were extracted from the FAERS database and 142 reports from the JADER database (Fig. 1).

Statistical analysis

The association between faricimab and AEs was assessed using statistical algorithms, including the Reporting Odds Ratio (ROR) [15], Proportional Reporting Ratio (PRR) [16], Bayesian Confidence Propagation Neural Network (BCPNN) [17], and Multi-Item Gamma Poisson Shrinker (MGPS) [18]. This analysis was grounded in disproportionality methods. Comprehensive details on the formulas and criteria applied in each algorithm are provided in (Table 1). Our investigation focused on AE signals that satisfied the specific thresholds set by each algorithm. Signals representing novel AEs were identified as any significant AE not previously listed in the product information (Full Prescribing Information, Revised: 07/2024). The onset time was defined as the interval between the occurrence of the AE (EVENT_DT) and the start of faricimab treatment (START_DT). Reports with erroneous data entries, such as an EVENT_DT preceding START_DT or containing invalid dates, were excluded from analysis. The onset time was summarized using the median and interquartile range (IQR). Statistical analyses and data processing were performed with R 4.3.3, Navicat Premium 15, and Microsoft Excel 2019.

Results

General characteristics

A total of 4234 and 142 reports related to faricimab were extracted from the FAERS and JADER databases, respectively. Demographic characteristics, including gender, age, weight, reporter occupation, country of origin, and clinical outcomes, are summarized in Table 2.

In both databases, the majority of reports involved patients aged 61–80 years, with a higher proportion of female cases in FAERS and male cases in JADER. The most commonly reported indication was neovascular age-related macular degeneration (nAMD).

The annual trend of reports is illustrated in Fig. 2, showing variations in reporting frequency over time.

Signal detection

Signals of system organ class (SOC)

Faricimab-related AEs exhibited varying signal strengths across different SOCs, as outlined in (Table 3). The analysis reveals that faricimab-related AEs impacted 26 organ systems in the FAERS database and 14 organ systems in the JADER database (Supplementary Table S1).

In the FAERS database, multiple SOCs showed statistically significant signals related to the faricimab. First, in the category of General Disorders and Administration Site Conditions, AE signals were noted as: n = 2296, ROR = 1.68. Second, in the category of Injury, Poisoning and Procedural Complications, AE reports were: n = 2004, ROR = 2.86. Lastly, in the Eye Disorders category, a very significant AE signal was observed, with report numbers of: n = 2920, ROR = 24.41.

In the JADER database, only one SOC showed a significant signal, which was Eye Disorders. which was Eye Disorders. In this category, AE signals were noted as: n = 138, ROR = 154.03.

Signals of preferred terms (PT)

FAERS In the FAERS database, four algorithms collectively identified 128 PT signals associated with faricimab, spanning 9 SOCs (Supplementary Table S2). The detailed screening process is illustrated in Fig. 3A. Table 4 summarizes post-marketing surveillance AEs reported at least 10 times, covering 63 PTs across 8 different SOCs.

When compared with the drug product insert, the matched positive signals include: cataract, conjunctival

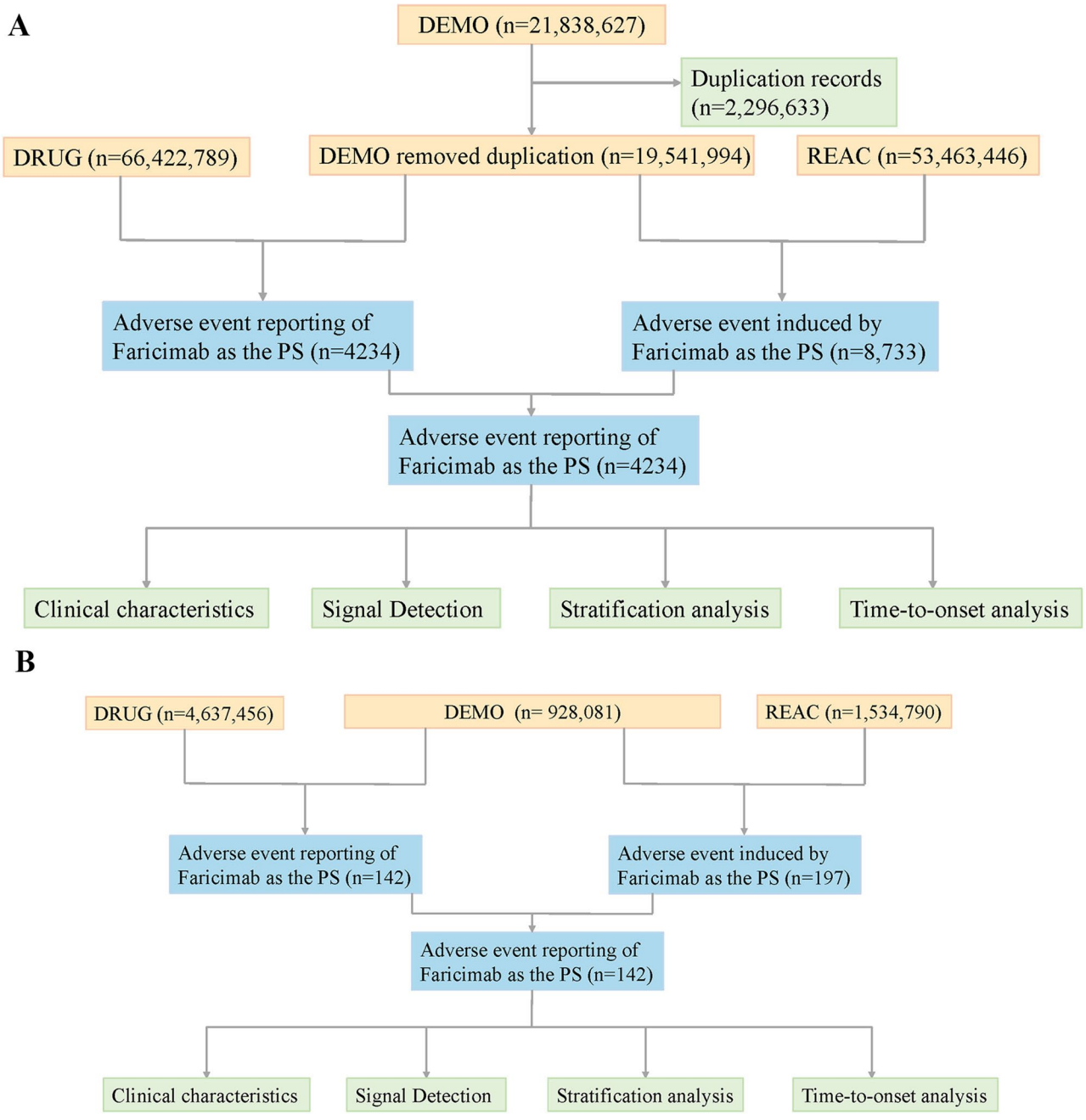

Fig. 1 **A** The process of selecting faricimab-associated AEs from FAERS database. **B** The process of selecting faricimab-associated AEs from JADER database

hemorrhage, vitreous detachment, vitreous opacities, retinal pigment epithelial tear, intraocular pressure increased, eye pain, eye inflammation, increased lacrimation, eye irritation, ocular discomfort, corneal abrasion, blurred vision, foreign body sensation, endophthalmitis, conjunctival hyperemia, visual acuity reduced, vitreous hemorrhage, retinal tear, and retinal detachment.

PTs listed in the product insert but not detected as positive signals in FAERS include: ocular pruritus, ocular hyperemia, and temporary vision decrease.

Additionally, the top 20 unmatched positive signals in FAERS, ranked by frequency, are: off-label use, no adverse event, visual impairment, uveitis, vitreous floaters, vitritis, vision blurred, iridocyclitis, blindness, retinal hemorrhage, eye disorder, iritis, inflammation, intercepted product storage error, retinal vasculitis, eye hemorrhage, anterior chamber inflammation, keratic precipitates, ocular hyperemia, and vitreous hemorrhage. Figure 4 A presents a forest plot of the top 30 PT signals by occurrence in FAERS.

Table 1 The specific formulas and positive criteria of the four algorithms

Algorithms	Equation	Criteria
ROR	ROR = ad/bc 95%CI = $e^{\ln(ROR)\pm1.96\sqrt{1/a+1/b+1/c+1/d}}$	Lower limit of 95% CI > 1, N ≥ 3
PRR	PRR = [a(c + d)]/[c(a + b)] $\chi^2 = [(ad-bc)^2](a+b+c+d)/[(a+b)(c+d)(a+c)(b+d)]$	PRR ≥ 2, $\chi^2 \geq 4$, N ≥ 3
BCPNN	$IC = \log_2 a(a+b+c+d)/[(a+c)(a+b)]$ $95\%CI = E(IC) \pm 2[V(IC)]^{0.5}$	IC025 > 0
MGPS	EBGM = a(a + b + c + d)/[(a + c)(a + b)] 95%CI = $e^{\ln(EBGM)\pm1.96\sqrt{1/a+1/b+1/c+1/d}}$	EBGM05 > 2

In FAERS, the five PTs with the highest ROR values are: Retinal occlusive vasculitis (n = 26, ROR = 1764.94); Macular thickening (n = 9, ROR = 1483.18); - Ocular vasculitis (n = 17, ROR = 934.71); Idiopathic orbital inflammation (n = 16, ROR = 768.81; Keratic precipitates (n = 37, ROR = 739.65).

JADER In the JADER database, four algorithms collectively identified 15 PT signals associated with faricimab, spanning 3 SOCs (Supplementary Table S2). The detailed screening process is illustrated in Fig. 3B. Table 4 summarizes post-marketing surveillance AEs reported at least 10 times, covering 6 PTs across 2 different SOCs.

When compared with the drug product insert, the matched positive signals include: retinal pigment epithelial tear, eye inflammation, retinal hemorrhage, retinal vasculitis, retinal vascular occlusion, retinal artery occlusion, retinal occlusive vasculitis, and endophthalmitis.

PTs detected as positive signals in JADER but not listed in the package insert include uveitis, anterior chamber inflammation, iridocyclitis, vitritis, iritis, non-infectious endophthalmitis, and cerebral infarction. Figure 4B presents the forest plot of all PT signals by occurrence in the JADER database.

PTs with the highest ROR values in the JADER database include: Retinal occlusive vasculitis (n = 3, ROR = 1695.04); Iridocyclitis (n = 8, ROR = 579.92); Retinal vascular occlusion (n = 6, ROR = 507.41).

Onset time of AEs

FAERS In the FAERS database, a total of 585 records contained precise data on the onset time of AEs. The median onset time was 87 days (IQR: 31–193 days).

A total of 443 cases (75.7%) occurred within the first 200 days of treatment. Specifically, 102 cases (17.4%) were reported within 0–20 days, 109 cases (18.6%) within 21–50 days, 110 cases (18.8%) within 51–100 days, and 122 cases (20.9%) within 101–200 days. Between 201 and 500 days, the frequency of AE reports gradually decreased, with 58 cases (9.9%) occurring between 201 and 300 days, 29 cases (5.0%) between 301 and 400 days, and 20 cases (3.4%) between 401 and 500 days. Additionally, 35 cases (6.0%) reported an onset time of over 500 days.

Figure 5A illustrates the distribution of AE onset times, showing that most cases occurred within the first 200 days of treatment.

JADER In the JADER database, there were 57 records with specific data on the onset time of AEs. The median onset time was 50 days (IQR: 17–112 days). A total of 52 cases (91.3%) occurred within the first 200 days of treatment. Specifically, 17 cases (29.8%) were reported within 0–20 days, 12 cases (21.1%) within 21–50 days, 9 cases (15.8%) within 51–100 days, and 14 cases (24.6%) within 101–200 days.

After 200 days of treatment, the number of AE reports gradually decreased, with 2 cases (3.5%) occurring between 201 and 300 days, 1 case (1.8%) between 301 and 400 days, 1 case (1.8%) between 401 and 500 days, and 1 case (1.8%) beyond 500 days. Figure 5B illustrates the distribution of AE onset times.

Subgroup analysis

Our study conducted a subgroup analysis of Faricimab-related AEs using data from the FAERS and JADER databases to explore risk patterns across different gender and age groups. The FAERS database includes both gender and age information, whereas JADER provides only gender data due to privacy protections. This analysis helps identify AE occurrence trends in specific populations, offering a more precise safety assessment for clinical use.

FAERS

Gender subgroup analysis The gender subgroup analysis based on the FAERS database identified differences in the occurrence of Faricimab-associated AEs between male and female patients. Our study analyzed all AEs for gender differences and presented the top 30 most frequently reported AEs in Fig. 6A.

The results show that certain AEs were more frequently reported in female patients, particularly those related to ocular inflammation. These included uveitis (ROR = 1.73), eye inflammation (ROR = 1.93), vitritis (ROR = 1.61), and iridocyclitis (ROR = 2.09), which had higher ROR values in female patients compared to males.

In contrast, male patients had a higher prevalence of certain AEs, including retinal vasculitis (ROR = 4.64), intraocular pressure increased (ROR = 1.44), and visual acuity reduced (ROR = 1.71).

Additionally, some AEs showed no significant gender-related differences, as their confidence intervals included 1. These included retinal hemorrhage (ROR = 0.68), eye pain (ROR = 0.88), and cataract (ROR = 1.11).

Table 2 General characteristics of reports with faricimab from the FAERS and JADER database

Characteristics	FAERS		JADER	
	Number	Proportion (%)	Number	Proportion (%)
Number of events	4234		142	
Gender				
Female	1707	40.3	53	37.3
Male	1524	36	78	54.9
Missing	1003	23.7	11	7.7
Weight				
<50 kg	17	0.4	4	2.8
50–80 kg	196	4.6	28	19.6
>80 kg	135	3.2	1	0.7
Missing	3886	91.8	109	76.8
Age				
<18 years	93	2.2	–	–
18–40 years	70	1.7	–	–
41–60 years	483	11.4	11	7.7
61–80 years	1332	31.5	81	57
≥81 years	563	13.3	40	28.2
Missing	1693	40	10	7
Occupation				
Medical doctor	2478	58.5	137	96.5
Consumer	1401	33.1	1	0.7
Health Professional	271	6.4	1	0.7
Pharmacist	77	1.8	3	2.1
Missing	7	0.2	0	0
Report country				
United States	2167	51.2	–	–
India	333	7.9	–	–
Japan	284	6.7	142	100
Canada	232	5.5	–	–
France	175	4.1	–	–
United Kingdom	173	4.1	–	–
Australia	140	3.3	–	–
Korea, South	121	2.9	–	–
Germany	90	2.1	–	–
South Africa	59	1.4	–	–
Outcome				
Hospitalization	170	4	–	–
Death	129	3	5	3.5
Disability	52	1.2	–	–
Life-threatening	17	0.4	–	–
Required Intervention	5	0.1	–	–
Outcome				
Congenital anomaly	2	0	–	–
Partially Recovered	–	–	40	28.2
Recovered	–	–	37	26.1
Not Recovered	–	–	35	24.6
Sequelae Present	–	–	6	4.2
Other	639	15.1	–	–
Missing	1014	23.9	19	13.4
Indications(top five)				
Neovascular age-related macular degeneration	1354	32	83	58.5
Product used for unknown indication	879	20.8	–	–
Diabetic retinal oedema	603	14.2	39	27.5

Table 2 (continued)

Characteristics	FAERS		JADER	
	Number	Proportion (%)	Number	Proportion (%)
Age-related macular degeneration	225	5.3	17	12
Retinal vein occlusion	202	4.8	1	0.7
Polypoidal choroidal vasculopathy	–	–	2	1.4

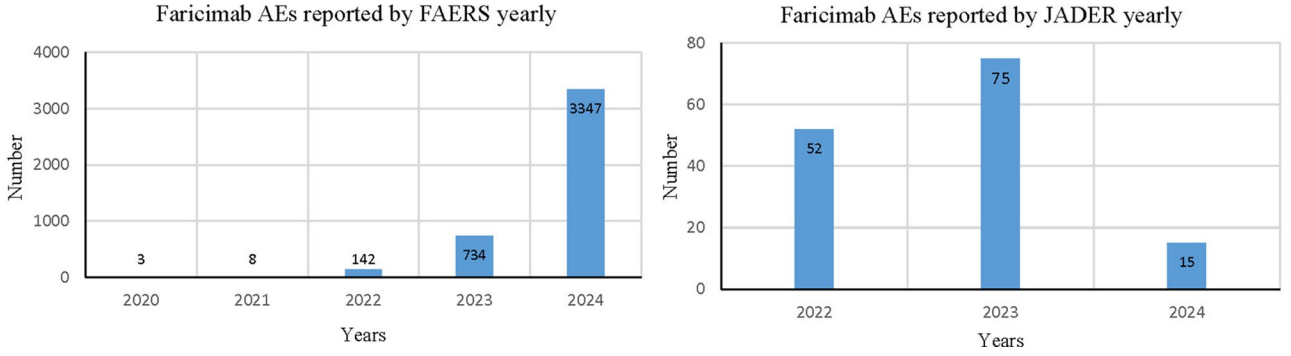

Fig. 2 The number of AEs reported by FAERS and JADER yearly

Table 3 Signal strength of reports of Faricimab at the SOC level in FAERS and JADER database

SOC	n	ROR (95%CI)	PRR (χ^2)	EBGM (EBGM05)	IC (IC025)
FAERS					
General disorders and administration site conditions	2296	1.68 (1.6–1.76)*	1.5 (460.72)	1.5 (1.44)	0.58 (0.52)*
Injury, poisoning and procedural complications	2004	2.86 (2.72–3.01)*	2.44 (1872.5)*	2.44 (2.34)*	1.28 (1.21)*
Eye disorders	2920	24.41 (23.35–25.52)*	16.58 (43516.93)*	16.54 (15.93)*	4.05 (3.99)*
JADER					
Eye disorders	138	154.03 (113.52–209)*	46.83 (6246.83)*	46.56 (34.31)*	5.54 (3.86)*

SOC system organ class; *n* the number of reports; *ROR* reporting odds ratio; *95%CI* 95% confidence interval; *PRR* proportional reporting ratio; χ^2 chi-squared; *IC* information component; *IC025* the lower limit of 95%CI of the IC; *EBGM* empirical Bayesian geometric mean; *EBGM05* the lower limit of 95%CI of EBGM

*Indicates statistically significant signals in algorithms. Notes: The SOCs that met at least one of the algorithm screening criterions are listed

Age subgroup analysis The age subgroup analysis based on the FAERS database identified differences in the occurrence of Faricimab-associated adverse events (AEs) between younger (<65 years) and older (≥65 years) patients. This study analyzed all AEs for age-related differences and presented the top 30 most frequently reported AEs in Fig. 6B.

The results show that certain AEs were more frequently reported in older patients (≥65 years), particularly those related to ocular inflammation. These included visual impairment (ROR = 0.48), vision blurred (ROR = 0.71), uveitis (ROR = 0.38), iridocyclitis (ROR = 0.29), vitritis (ROR = 0.21), and eye inflammation (ROR = 0.24). Most of these AEs were inflammation-related, with ROR values below 1, indicating a lower reporting frequency in older patients.

In contrast, certain AEs were more frequently reported in younger patients (<65 years), including vitreous hemorrhage (ROR = 2.36), cataract (ROR = 1.77), and lacrimation increased (ROR = 1.14). Among these, vitreous hemorrhage had the highest ROR in younger patients.

Additionally, some AEs showed no significant age-related differences, as their confidence intervals included 1. These included retinal vasculitis (ROR = 0.34), retinal artery occlusion (ROR = 1.06), eye pain (ROR = 0.51), and retinal occlusive vasculitis (ROR = 0.81).

JADER

The gender subgroup analysis in the JADER database identified differences in the occurrence of Faricimab-associated AEs between male and female patients (Table 5).

Some AEs were reported in both male and female patients, primarily involving eye inflammation and retinal vascular abnormalities. However, the ROR was generally higher in female patients, especially for eye inflammation (ROR = 2359.79), anterior chamber inflammation (ROR = 743.13), vitritis (ROR = 538.93), retinal pigment epithelial tear (ROR = 1486.35), and iridocyclitis (ROR = 845.47).

Certain AEs were more frequently reported in male patients, particularly those related to systemic vascular and retinal vascular events. For example, cerebral infarction (ROR = 13.19) had a higher ROR in males compared to females (ROR = 7.16). Additionally, retinal vascular

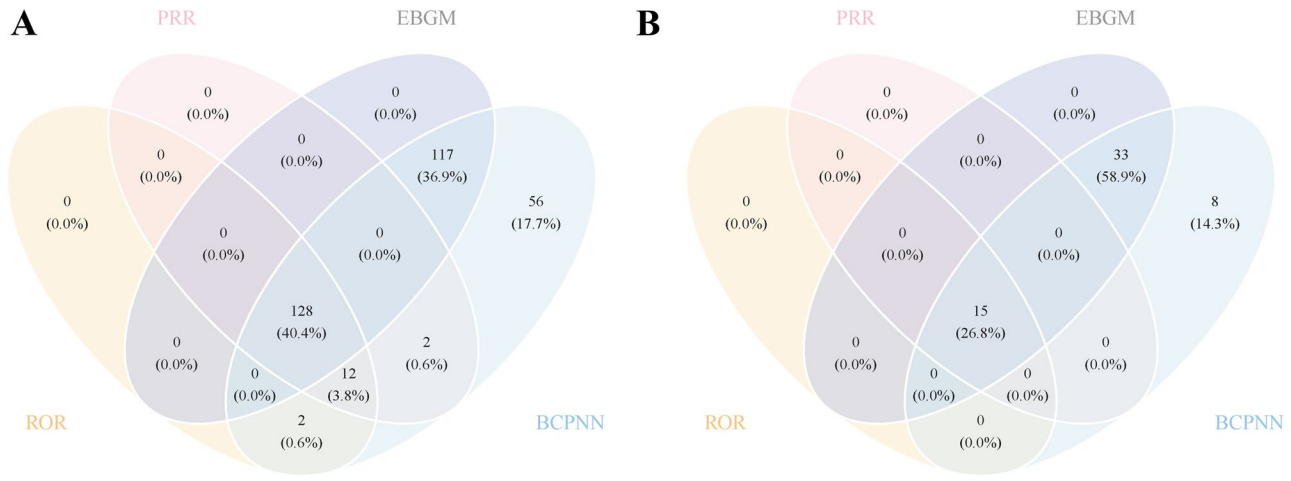

Fig. 3 **A** Venn diagram for the screening of all FAERS PTs based on the results of the four algorithms. **B** Venn diagram for the screening of all JADER PTs based on the results of the four algorithms

occlusion (ROR = 485.74, 95% CI 173.1–1363.02) was observed in males, while no significant reports were found in females. Endophthalmitis (ROR = 188.07) and retinal hemorrhage (ROR = 85.27) were also reported in males but not significantly in females.

Retinal occlusive vasculitis (ROR = 15630.21) had the highest ROR in female patients, with no significant reports in males. This trend was also observed for other inflammatory AEs, where female patients showed consistently higher ROR values. Conversely, male patients exhibited a higher prevalence of retinal vascular and systemic vascular events, including retinal vascular occlusion (ROR = 485.74) and cerebral infarction (ROR = 13.19).

These variations in AE distribution across subgroups will be further analyzed in the Discussion section.

Discussion

Research innovations

This study systematically analyzed the real-world safety profile of faricimab using data from FAERS and JADER pharmacovigilance databases, introducing several key innovations in data sources, analytical methods, and risk assessment.

Firstly, this is the first systematic cross-database validation of faricimab-associated AEs, comparing FAERS and JADER to assess signal consistency across regulatory systems and regional populations. By incorporating JADER data, this study provides new safety insights for Asian populations, aiding global pharmacovigilance and identifying regional variations in AE reporting.

Secondly, this study identified previously unreported PT signals [6, 10], including keratic precipitates (ROR = 739.65), visual field defect (ROR = 6.46), macular hole (ROR = 30.84), epiretinal membrane (ROR = 191.66), macular ischemia (ROR = 260.46), optic nerve injury (ROR = 18.41), and optic disc disorder (ROR = 90.94). These findings suggest potential updates to faricimab's safety labeling and emphasize the need for closer clinical monitoring, particularly for retinal and optic nerve-related complications.

Thirdly, subgroup analyses revealed age- and sex-related differences in AE occurrence, identifying high-risk populations and supporting personalized pharmacovigilance strategies. Unlike prior research, this study systematically examined AE trends across different demographics using both FAERS and JADER datasets.

Additionally, this study investigated the temporal distribution of AEs, distinguishing between early-onset and delayed-onset reactions. This novel approach optimizes AE monitoring windows and informs long-term follow-up strategies.

Finally, in contrast to previous studies that focused on common AEs (e.g., retinal hemorrhage, inflammation), this study uncovered new AE signals not listed in prescribing information, providing valuable evidence for future drug regulation and clinical safety monitoring.

New results

Overall AE signal analysis

SOC-level AE signal analysis At the SOC level, multiple categories of AEs exhibited significant positive signals in both the FAERS and JADER databases. Among these, Eye Disorders emerged as the most significant AE category. In the JADER database, 138 cases of Eye Disorders were reported, with an ROR of 154.03. In the FAERS database, the number of reported Eye Disorder AEs was even higher, reaching 2920 cases, with an ROR of 24.41. This strongly positive signal confirms that ocular AEs are a primary safety concern for faricimab, suggesting that the drug may

Table 4 Signal strength of reports of Faricimab at the PT level in FAERS and JADER database

SOC	PT	n	ROR (95%CI)
FAERS			
Injury, poisoning and procedural complications	Off label use	1730	18.24 (17.31–19.23)
	Intercepted product storage error	53	137.51 (104.65–180.68)
	Product prescribing error	14	4.41 (2.61–7.45)
	Intra-ocular injection complication	10	367.36 (193.99–695.68)
General disorders and administration site conditions	No adverse event	1648	86.99 (82.43–91.81)
	Inflammation	59	8.27 (6.4–10.69)
Eye disorders	Visual impairment	265	15.75 (13.93–17.8)
	Uveitis	211	117.08 (102–134.38)
	Eye inflammation	196	159.85 (138.5–184.49)
	Vitreous floaters	150	114.09 (96.94–134.27)
	Vitritis	145	663.8 (558.58–788.83)
	Vision blurred	132	6.81 (5.73–8.09)
	Iridocyclitis	121	304.05 (253.02–365.38)
	Blindness	109	19.06 (15.77–23.02)
	Eye pain	94	12.53 (10.22–15.35)
	Visual acuity reduced	90	17.52 (14.23–21.57)
	Retinal haemorrhage	73	71.83 (56.97–90.56)
	Eye disorder	64	13.7 (10.71–17.52)
	Iritis	59	134 (103.45–173.58)
	Cataract	56	6.72 (5.17–8.74)
	Retinal pigment epithelial tear	43	449.94 (329.88–613.71)
	Retinal vasculitis	38	243.68 (176.08–337.23)
	Eye haemorrhage	38	19.23 (13.97–26.46)
	Anterior chamber inflammation	37	481.56 (344.37–673.41)
	Keratic precipitates	37	739.65 (525.52–1041.04)
	Ocular hyperaemia	37	5.83 (4.22–8.05)
	Vitreous haemorrhage	35	88.23 (63.15–123.26)
	Dry eye	30	4.83 (3.37–6.91)
	Diabetic retinopathy	29	59.04 (40.93–85.15)
	Eye irritation	29	4 (2.78–5.76)
	Lacrimation increased	27	6.56 (4.49–9.57)
	Retinal occlusive vasculitis	26	1764.94 (1140.22–2731.94)
	Vitreous opacities	25	216.62 (145.28–322.98)
	Corneal oedema	23	70.41 (46.65–106.26)
	Retinal artery occlusion	21	60.42 (39.29–92.92)
SOC	**PT**	**n**	**ROR(95%CI)**
FAERS			
Eye disorders	Photophobia	21	7.93 (5.17–12.17)
	Neovascular age-related macular degeneration	19	107.99 (68.58–170.06)
	Blindness unilateral	19	9.38 (5.98–14.72)
	Foreign body sensation in eyes	19	21.78 (13.87–34.19)
	Glaucoma	17	6.05 (3.76–9.74)
	Ocular vasculitis	17	934.71 (560.78–1557.97)
	Retinal vein occlusion	16	39.87 (24.37–65.21)
	Subretinal fluid	16	121.89 (74.28–200.03)
	Anterior chamber cell	16	161.38 (98.19–265.25)
	Idiopathic orbital inflammation	16	768.81 (456.9–1293.64)
	Non-infectious endophthalmitis	15	126.59 (75.89–211.17)
	Ocular hypertension	15	57.53 (34.58–95.69)
	Metamorphopsia	14	52.76 (31.16–89.32)
	Eye discharge	14	10.11 (5.98–17.09)
	Vitreal cells	13	574.67 (325.31–1015.17)

Table 4 (continued)

SOC	PT	n	ROR (95%CI)
	Photopsia	12	12.99 (7.37–22.9)
	Macular degeneration	10	5.93 (3.19–11.02)
	Retinal vascular occlusion	10	93.39 (49.99–174.45)
	Ocular discomfort	10	7.17 (3.85–13.34)
Infections and infestations	Endophthalmitis	154	187.58 (159.58–220.51)
	Suspected transmission of an infectious agent via product	27	155.93 (106.36–228.59)
	Hypopyon	22	190.56 (124.6–291.44)
	Eye infection	17	10.76 (6.69–17.33)
	Chorioretinitis	16	194.11 (117.95–319.45)
Investigations	Intraocular pressure increased	95	50.61 (41.32–62.01)
Vascular disorders	Vasculitis	29	17.14 (11.9–24.69)
Nervous system disorders	Cerebral infarction	18	4.96 (3.12–7.88)
Product issues	Product complaint	11	3.45 (1.91–6.23)
JADER			
Eye disorders	Retinal pigment epithelial tear	25	1245.95 (798.94–1943.07)
	Eye inflammation	15	1561.37 (883.19–2760.29)
	Uveitis	15	139.36 (81.99–236.89)
	Anterior chamber inflammation	11	384.5 (206.54–715.77)
	Retinal haemorrhage	10	68.45 (36.14–129.64)
Nervous system disorders	Cerebral infarction	13	10.35 (5.89–18.16)

SOC system organ class; *PT* preferred term; *n* the number of reports; *ROR* reporting odds ratio; *95%CI* 95% confidence interval. Notes: The PTs with n ≥ 10 and met the four algorithm screening criterions are listed

lead to retinal, corneal, and other ocular complications in certain patients.

Apart from ocular AEs, General Disorders and Administration Site Conditions also showed a positive signal in the FAERS database, with 2296 cases, ROR of 1.68. Although the ROR value is relatively low, it still indicates a potential association between faricimab and administration site reactions related to intravitreal injection. Additionally, Injury, Poisoning, and Procedural Complications exhibited a higher positive signal (n = 2004, ROR = 2.86), suggesting that the administration method of faricimab may pose certain procedural risks.

Moreover, several SOC categories exhibited a relatively high number of reported AEs in the FAERS database, but their signal strength did not reach the positive threshold, including Infections and Infestations (n = 361), Nervous System Disorders (n = 251), Gastrointestinal Disorders (n = 73), and Ear and Labyrinth Disorders (n = 37). While these categories had a substantial number of reports, they did not meet statistical significance across multiple signal detection algorithms, suggesting that their association with faricimab may be weaker or that their clinical relevance remains uncertain and requires further investigation.

Comparisons between the FAERS and JADER databases revealed certain discrepancies in SOC-level signals. The FAERS database generally reported a higher number of AEs compared to JADER, likely due to the fact that FAERS includes consumer reports, while JADER primarily consists of reports from healthcare institutions. As a result, FAERS may capture a broader spectrum of AEs, whereas JADER may focus on clinically recognized severe AEs. Furthermore, the stronger signal for General Disorders in FAERS may reflect a greater emphasis on monitoring injection-related AEs within the U.S. pharmacovigilance system [19, 20]. Conversely, certain ocular AEs showed a stronger signal in JADER, suggesting potential differences in faricimab-related safety profiles among Asian populations. These findings highlight the importance of considering reporting biases and database-specific characteristics when evaluating AE signals across different pharmacovigilance systems.

PT-level AE signal analysis Building on the SOC-level analysis, we further investigated specific PT-level AE signals within each SOC category. Through manual screening and Bonferroni correction, several previously unreported PT signals were identified, most of which were related to Eye Disorders. All PT signals were calibrated using the Bonferroni correction (Supplementary Table S3).

Among the newly identified PT signals, keratic precipitates exhibited the strongest signal, with 37 cases, ROR = 739.65, suggesting that faricimab may induce corneal inflammatory reactions in some patients. Additionally, macular ischemia demonstrated a highly positive signal (n = 5, ROR = 260.46), which may be associated with vascular perfusion abnormalities due to VEGF suppression, raising concerns about the drug's impact on retinal circulation.

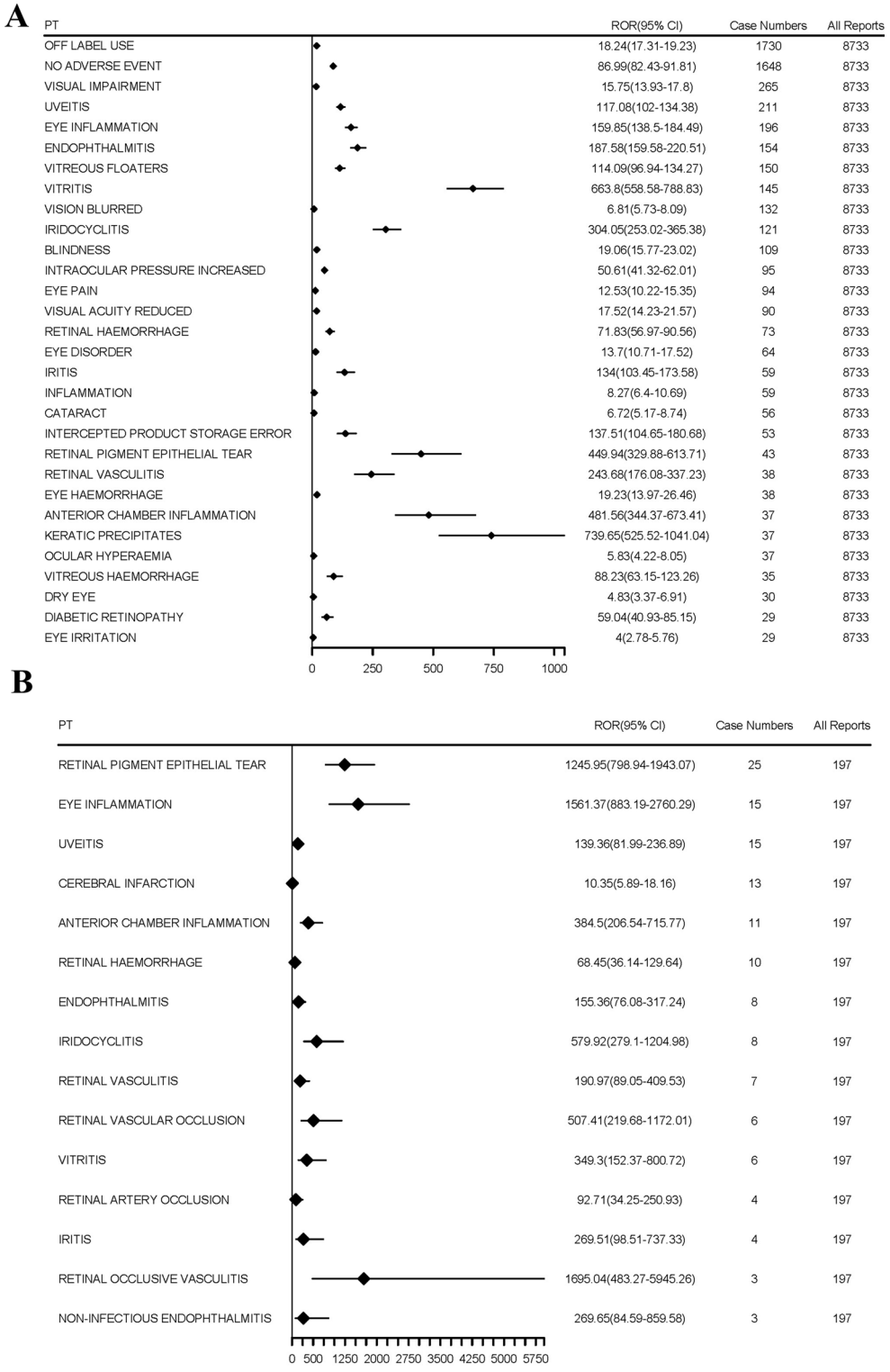

Fig. 4 **A** Forest plot of the top 30 PT signals by occurrence in the FAERS database. **B** Forest plot of all PT signals by occurrence in the JADER database

Other notable AE signals included optic nerve injury (n = 3, ROR = 18.41), which may be linked to the effects of VEGF and Ang-2 dual inhibition on optic nerve blood supply. Furthermore, macular hole (n = 6, ROR = 30.84) and epiretinal membrane (n = 5, ROR = 191.66) may be associated with alterations in retinal tissue stability during the post-treatment repair process. These newly detected AE signals suggest that faricimab may influence

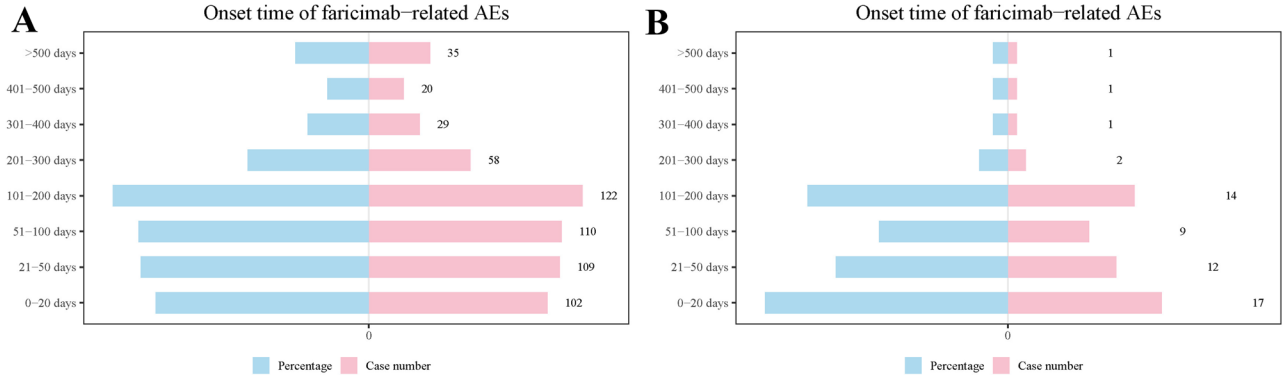

Fig. 5 **A** Onset time of faricimab-related AEs from FAERS. **B** Onset time of faricimab-related AEs from JADER

A

SOC	PT	FEMLAE/MALE	ROR(95% CI)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	OFF LABEL USE	797 / 796	0.75(0.67-0.83)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	NO ADVERSE EVENT	633 / 710	0.65(0.58-0.74)
EYE DISORDERS	VISUAL IMPAIRMENT	135 / 89	1.21(0.93-1.59)
EYE DISORDERS	UVEITIS	99 / 46	1.73(1.22-2.46)
EYE DISORDERS	EYE INFLAMMATION	84 / 35	1.93(1.3-2.87)
EYE DISORDERS	VITRITIS	76 / 38	1.6(1.08-2.37)
EYE DISORDERS	IRIDOCYCLITIS	73 / 28	2.09(1.35-3.25)
EYE DISORDERS	VISION BLURRED	73 / 45	1.3(0.89-1.88)
INFECTIONS AND INFESTATIONS	ENDOPHTHALMITIS	63 / 38	1.32(0.88-1.99)
EYE DISORDERS	VITREOUS FLOATERS	59 / 38	1.24(0.82-1.87)
EYE DISORDERS	VISUAL ACUITY REDUCED	51 / 24	1.7(1.04-2.77)
EYE DISORDERS	BLINDNESS	50 / 29	1.38(0.87-2.18)
INVESTIGATIONS	INTRAOCULAR PRESSURE INCREASED	45 / 25	1.44(0.88-2.35)
EYE DISORDERS	EYE PAIN	43 / 39	0.88(0.57-1.35)
EYE DISORDERS	RETINAL HAEMORRHAGE	30 / 35	0.68(0.42-1.11)
EYE DISORDERS	RETINAL VASCULITIS	29 / 5	4.64(1.79-12)
EYE DISORDERS	IRITIS	27 / 14	1.54(0.81-2.94)
EYE DISORDERS	CATARACT	25 / 18	1.11(0.6-2.03)
EYE DISORDERS	EYE DISORDER	25 / 29	0.68(0.4-1.17)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	INFLAMMATION	23 / 16	1.14(0.6-2.17)
EYE DISORDERS	OCULAR HYPERAEMIA	20 / 13	1.23(0.61-2.47)
EYE DISORDERS	ANTERIOR CHAMBER INFLAMMATION	18 / 7	2.05(0.86-4.92)
EYE DISORDERS	VITREOUS HAEMORRHAGE	18 / 7	2.05(0.86-4.92)
EYE DISORDERS	KERATIC PRECIPITATES	18 / 8	1.79(0.78-4.13)
EYE DISORDERS	EYE HAEMORRHAGE	17 / 15	0.9(0.45-1.81)
EYE DISORDERS	RETINAL PIGMENT EPITHELIAL TEAR	16 / 17	0.75(0.38-1.48)
EYE DISORDERS	RETINAL OCCLUSIVE VASCULITIS	16 / 7	1.82(0.75-4.43)
EYE DISORDERS	EYE IRRITATION	15 / 8	1.49(0.63-3.53)
EYE DISORDERS	VITREOUS OPACITIES	13 / 8	1.29(0.54-3.13)
INFECTIONS AND INFESTATIONS	SUSPECTED TRANSMISSION OF AN INFECTIOUS AGENT VIA PRODUCT	13 / 6	1.73(0.66-4.55)

B

SOC	PT	YOUNG/OLD	ROR(95% CI)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	OFF LABEL USE	572 / 827	1.68(1.48-1.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	NO ADVERSE EVENT	548 / 646	2.14(1.88-2.44)
EYE DISORDERS	VISUAL IMPAIRMENT	31 / 134	0.48(0.32-0.71)
EYE DISORDERS	VISION BLURRED	23 / 68	0.71(0.44-1.15)
INVESTIGATIONS	INTRAOCULAR PRESSURE INCREASED	18 / 35	1.09(0.62-1.93)
EYE DISORDERS	UVEITIS	17 / 94	0.38(0.22-0.63)
INFECTIONS AND INFESTATIONS	ENDOPHTHALMITIS	16 / 55	0.61(0.35-1.07)
EYE DISORDERS	CATARACT	15 / 18	1.77(0.89-3.52)
EYE DISORDERS	VISUAL ACUITY REDUCED	13 / 46	0.6(0.32-1.11)
EYE DISORDERS	BLINDNESS	12 / 37	0.68(0.36-1.32)
EYE DISORDERS	EYE PAIN	12 / 50	0.51(0.27-0.95)
EYE DISORDERS	RETINAL HAEMORRHAGE	11 / 34	0.68(0.35-1.35)
EYE DISORDERS	VITREOUS FLOATERS	11 / 52	0.44(0.23-0.85)
EYE DISORDERS	IRIDOCYCLITIS	10 / 72	0.29(0.15-0.56)
EYE DISORDERS	VITREOUS HAEMORRHAGE	10 / 9	2.36(0.96-5.82)
EYE DISORDERS	OCULAR HYPERAEMIA	9 / 19	1(0.45-2.22)
EYE DISORDERS	VITRITIS	8 / 79	0.21(0.1-0.44)
EYE DISORDERS	LACRIMATION INCREASED	7 / 13	1.14(0.45-2.86)
EYE DISORDERS	IRITIS	7 / 26	0.57(0.25-1.31)
EYE DISORDERS	EYE INFLAMMATION	7 / 62	0.24(0.11-0.52)
EYE DISORDERS	EYE DISORDER	7 / 22	0.67(0.29-1.58)
EYE DISORDERS	VITREOUS OPACITIES	6 / 12	1.06(0.4-2.83)
EYE DISORDERS	PHOTOPHOBIA	5 / 9	1.18(0.39-3.52)
EYE DISORDERS	RETINAL ARTERY OCCLUSION	5 / 10	1.06(0.36-3.1)
INFECTIONS AND INFESTATIONS	SUSPECTED TRANSMISSION OF AN INFECTIOUS AGENT VIA PRODUCT	5 / 11	0.96(0.33-2.77)
EYE DISORDERS	RETINAL OCCLUSIVE VASCULITIS	5 / 13	0.81(0.29-2.29)
EYE DISORDERS	ANTERIOR CHAMBER INFLAMMATION	4 / 13	0.65(0.21-2)
EYE DISORDERS	RETINAL VASCULITIS	4 / 25	0.34(0.12-0.97)
EYE DISORDERS	EYE HAEMORRHAGE	3 / 18	0.35(0.1-1.2)
VASCULAR DISORDERS	VASCULITIS	3 / 9	0.71(0.19-2.61)

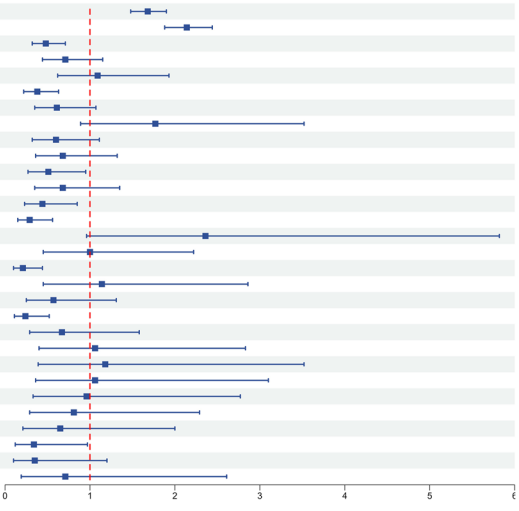

Fig. 6 **A** Gender subgroup analysis of Faricimab-associated AEs in the FAERS database, comparing AE occurrences between male and female patients, with the top 30 most frequently reported AEs displayed. **B** Age subgroup analysis of Faricimab-associated AEs in the FAERS database, comparing younger (<65 years) and older (≥65 years) patients, with the top 30 most frequently reported AEs displayed. The forest plot presents the reporting odds ratio (ROR) with 95% confidence intervals (CI), highlighting subgroup differences

Table 5 The gender subgroup analysis in the JADER database identified differences in the occurrence of Faricimab-associated AEs between male and female patients

PT	SOC	n	ROR(95% CI)
Male			
Retinal pigment epithelial tear	Eye disorders	15	915.83 (517.11–1621.98)
Uveitis	Eye disorders	10	150.55 (78.15–290.01)
Cerebral infarction	Nervous system disorders	10	13.19 (6.88–25.26)
Retinal haemorrhage	Eye disorders	8	85.27 (41.37–175.73)
Eye inflammation	Eye disorders	7	1165.8 (512.06–2654.14)
Endophthalmitis	Infections and infestations	6	188.07 (81.76–432.59)
Retinal vascular occlusion	Eye disorders	4	485.74 (173.1–1363.02)
Iridocyclitis	Eye disorders	4	445.92 (159.35–1247.88)
Retinal vasculitis	Eye disorders	4	153.66 (56.03–421.37)
Vitritis	Eye disorders	3	252.67 (78.59–812.32)
Anterior chamber inflammation	Eye disorders	3	157.91 (49.5–503.75)
Female			
Eye inflammation	Eye disorders	8	2359.79 (1060.65–5250.19)
Anterior chamber inflammation	Eye disorders	7	743.13 (333.27–1657.04)
Retinal pigment epithelial tear	Eye disorders	7	1486.35 (651.61–3390.44)
Uveitis	Eye disorders	4	104.85 (38.1–288.54)
Iridocyclitis	Eye disorders	4	845.47 (297.33–2404.1)
Retinal vasculitis	Eye disorders	3	267.14 (82.96–860.21)
Vitritis	Eye disorders	3	538.93 (165.01–1760.19)
Retinal occlusive vasculitis	Eye disorders	3	15630.21 (2572.61–94963.35)
Cerebral infarction	Nervous system disorders	3	7.16 (2.25–22.74)

the structural integrity of the retina, warranting further clinical investigation and monitoring.

At the PT level, there were also discrepancies between FAERS and JADER data. Certain AEs, such as macular ischemia and keratic precipitates, exhibited a stronger signal in the JADER database, implying that these AEs may be more prevalent among Asian populations [21]. Conversely, the FAERS database contained a larger volume of reports but demonstrated lower ROR values for some AEs, such as macular ischemia, possibly due to the influence of consumer reports. These findings underscore the importance of considering differences in data sources when evaluating AE signals, as variations in reporting mechanisms, patient demographics, and healthcare practices may impact the interpretation of pharmacovigilance data.

FAERS vs. JADER data comparison

Our study compared PT-level AE signals associated with faricimab in the FAERS and JADER databases and identified notable differences in signal strength between the two datasets. These differences not only reflect variations in reporting mechanisms and data sources but also suggest that Asian patients may exhibit a distinct AE occurrence pattern, warranting further investigation.

One of the most pronounced differences was observed in retinal pigment epithelial tear, where the ROR in JADER was significantly higher than in FAERS, suggesting that this AE may be more frequently reported in Asian patients. This observation could be attributed to structural differences in the retina among ethnic groups. Previous studies have indicated that the thickness of the retinal pigment epithelium in the macular region varies across populations, potentially making Asian patients more susceptible to retinal stress induced by VEGF/Ang-2 inhibition [22, 23]. Additionally, because JADER primarily consists of reports submitted by healthcare professionals, it is more likely to capture clinically confirmed and severe AEs, which may explain the stronger signal for retinal pigment epithelial tear in JADER compared to FAERS.

Another significant difference was observed in retinal vascular occlusion, where the signal strength in JADER was markedly higher than in FAERS, suggesting that Asian patients may have a higher susceptibility to retinal vascular events. The underlying mechanisms could involve genetic predisposition and vascular physiology. Studies have suggested that Asian populations tend to have higher renin-angiotensin system activity, which could increase the risk of vascular occlusion following VEGF/Ang-2 inhibition [24–26]. Furthermore, since JADER reports are predominantly submitted by physicians, there may be a greater emphasis on retinal hemodynamic abnormalities, leading to a higher reporting rate for retinal vascular occlusion. In contrast, FAERS includes a broader range of spontaneous reports, which could dilute the signal strength for this AE due to underreporting by physicians.

In the case of vitritis, the number of reports in FAERS was significantly higher than in JADER, suggesting that Western patients may be more likely to report this AE, or that this AE is more noticeable to patients themselves. The FAERS database allows both patients and healthcare professionals to submit reports, and patients are generally more sensitive to ocular inflammation symptoms, which may lead to an exaggeration of the vitritis signal in FAERS. Conversely, JADER primarily includes physician-reported AEs, which may focus more on severe ocular inflammation, such as uveitis, while mild cases of vitritis may not be separately recorded.

Additionally, macular ischemia exhibited a stronger signal in FAERS than in JADER, suggesting that this AE may be more frequently detected in long-term follow-up settings. The FAERS database covers a wider patient population, including those undergoing prolonged VEGF/Ang-2 inhibition therapy, making it more sensitive to capturing chronic macular ischemia cases. In contrast, JADER primarily collects AEs that physicians deem clinically significant, which may lead to a preference for reporting acute and severe retinal events rather than chronic ischemia.

The variations in AE signals across the two databases may be attributed to multiple factors. First, FAERS allows consumers to report AEs, making it more likely to capture subjectively perceived AEs (e.g., inflammation and ocular discomfort). However, this also introduces the potential for overestimated signal strength due to non-professional reporting. In contrast, JADER exclusively consists of reports from healthcare institutions, which generally results in higher data quality but also a greater focus on clinically significant AEs, leading to stronger signals for specific AEs, such as retinal damage and vascular events.

Second, regional differences in patient physiology may influence AE distribution patterns. The JADER database primarily represents Asian patients, whereas FAERS encompasses a more diverse, multiethnic population. These demographic differences could impact the statistical representation of AE occurrence. For instance, Asian patients may exhibit unique retinal structural and vascular physiological characteristics, which could lead to differential AE responses to VEGF/Ang-2 inhibition when compared to Western populations.

Additionally, differences in healthcare systems may influence AE reporting trends. In the United States, regulatory monitoring of intravitreal injection-related AEs is more stringent, leading to a stronger signal for injection-site AEs (such as vitritis) in FAERS. In contrast, Japan's healthcare system tends to prioritize reporting severe AEs, which could explain why JADER exhibits stronger signals for structural damage AEs, such as retinal vascular occlusion and retinal pigment epithelial tear. These variations in regulatory focus and clinical reporting standards further contribute to the divergence in AE signal distribution between FAERS and JADER.

Subgroup analysis

Gender subgroup analysis

FAERS database Female patients were more likely to experience inflammation-related AEs, such as uveitis, eye inflammation, and vitritis. This trend may be related to greater immune sensitivity in females to VEGF/Ang-2 inhibitors. Women have a higher prevalence of immune-mediated diseases (e.g., autoimmune disorders), which may explain why they are more prone to inflammatory AEs following anti-VEGF/Ang-2 therapy [27, 28].
Male patients exhibited a higher incidence of retinal vascular-related AEs, including retinal vasculitis and retinal vascular occlusion. This may be associated with vascular structural characteristics and hemodynamic differences. Studies indicate that males generally have greater arterial stiffness and higher shear stress, which may lead to increased susceptibility to retinal vascular damage or occlusion following VEGF/Ang-2 inhibition [29, 30].

JADER database In the JADER database, the signal for inflammatory AEs was stronger in female patients, further supporting the hypothesis that females are more sensitive to VEGF/Ang-2 inhibition and more likely to develop immune-mediated inflammation. Additionally, Asian females may exhibit specific immune response patterns, which could explain why the signal strength for inflammatory AEs is stronger in JADER than in FAERS.

Male patients in JADER showed a higher incidence of retinal vascular events, such as vascular occlusion and thrombosis, suggesting that Asian males may have a greater predisposition to vascular diseases. Previous studies have indicated that Asian males have a higher cardiovascular disease risk, which may also affect retinal vascular health, thereby increasing the likelihood of retinal vascular events following VEGF/Ang-2 inhibition [31, 32].

Age subgroup analysis Older patients (≥65 years) had a lower incidence of inflammation-related AEs, possibly due to immune senescence, a decline in immune system activity with aging [33]. This may lead to a reduced inflammatory response, resulting in a lower occurrence of uveitis and eye inflammation.

In contrast, younger patients (<65 years) were more likely to develop vitreous hemorrhage and macular ischemia, both of which are vascular-related AEs. This may be due to higher vascular activity and metabolic rates in younger individuals [34]. Since VEGF inhibition can impact retinal blood flow, younger patients may be more susceptible to retinal ischemia. Additionally, research suggests that the retinal microcirculation in younger patients is more responsive to VEGF regulation, making it more vulnerable to damage from VEGF/Ang-2 inhibition.

The trends in age-related AEs were consistent across FAERS and JADER, indicating that younger patients are more likely to experience acute retinal vascular events, whereas older patients are more prone to chronic retinal conditions.

Implications for clinical practice

This study, based on the FAERS and JADER databases, analyzed adverse events (AEs) associated with faricimab and identified high-risk populations. The findings provide valuable insights for optimizing dosing strategies, individualized AE monitoring, and adjunctive therapies to enhance patient safety and treatment outcomes.

Optimizing dosing strategies

Increased vigilance is recommended for patients presenting with symptoms suggestive of macular ischemia, optic nerve dysfunction, or epiretinal changes, as these events were newly detected in pharmacovigilance data. Based on these findings, individualized dose adjustments may help reduce the risk of AEs. It is recommended to initiate treatment with a lower dose, gradually adjusting based on patient response. For high-risk patients, such as older individuals or those with pre-existing retinal vascular conditions, extending follow-up intervals may allow for early detection and intervention for potential AEs [35].

Sex-based differences should be considered when prescribing faricimab. Female patients are more prone to inflammatory AEs, such as uveitis and vitritis, necessitating closer monitoring during the initial treatment phase and potential adjunctive anti-inflammatory therapy. In contrast, male patients are more susceptible to retinal vascular occlusion, warranting regular monitoring of intraocular pressure and retinal perfusion to reduce thrombotic risk [36, 37].

Individualized AE monitoring

The incidence of AEs varies significantly across different age groups, making personalized monitoring strategies essential for optimizing patient safety. Current drug safety guidelines lack specific follow-up schedules for high-risk patients, whereas our findings propose more specific monitoring strategies. However, these strategies are yet to be validated and may become a potential update to drug safety guidelines.

For older patients (≥65 years), the risk of inflammation-related AEs is lower, likely due to immunosenescence, the age-related decline in immune function. However, they face a higher risk of retinal atrophy and optic nerve damage. Regular vision assessments are recommended, including visual acuity testing every 3–6 months, visual field examinations every 6–12 months, and OCT evaluation of the retinal nerve fiber layer thickness. Since VEGF/Ang-2 inhibition may accelerate cataract progression, lens status should be evaluated every 6–12 months, with surgical intervention planned as needed [38].

For younger patients (<65 years), particularly those with diabetes, there is a higher likelihood of vitreous hemorrhage and macular ischemia. It is advisable to perform OCTA and FFA every 3–6 months to monitor retinal perfusion. Diabetic patients should have more frequent follow-ups, every 2–3 months, to enable early detection and intervention for ischemic retinal damage [39, 40]. For high-risk patients, such as those with a history of vitreous hemorrhage, evaluating intraocular hemorrhage during each follow-up is recommended, along with potential adjustments to anti-VEGF therapy or the addition of anticoagulant/anti-inflammatory treatment when necessary.

Gender differences should also be considered. Female patients are at a higher risk of inflammation-related AEs, so it is recommended to conduct follow-ups every 4 weeks during the first 3 months of treatment. If signs of inflammation appear, early initiation of local anti-inflammatory therapy, such as NSAIDs or low-dose corticosteroid eye drops, may be warranted [41]. Male patients are more prone to retinal vascular occlusion, especially those with hypertension, diabetes, or cardiovascular disease. For these individuals, OCT-A monitoring every 3 months is advised, and in patients with a high risk of thrombosis, personalized adjustments to anti-VEGF dosage should be considered [42, 43].

Personalized monitoring strategies should be tailored by clinicians based on patients' underlying conditions, treatment history, disease progression, and high-risk factors such as age, gender, and comorbidities, ensuring optimal therapeutic outcomes while minimizing the risk of adverse events. For elderly patients (≥65 years), regular vision tests, visual field assessments, and OCT evaluations are necessary to monitor retinal atrophy and optic nerve damage. Younger diabetic patients (<65 years) are at higher risk of vitreous hemorrhage and macular ischemia, requiring OCTA and FFA screenings every 3–6 months and follow-ups every 2–3 months. High-risk patients with a history of vitreous hemorrhage should have intraocular hemorrhage evaluated at each visit, with therapy adjustments as needed. Female patients, prone to inflammation-related adverse events, should be monitored every 4 weeks during the initial phase and receive anti-inflammatory treatment if needed. Male patients, particularly those with hypertension, diabetes, or cardiovascular disease, should undergo OCT-A monitoring every 3 months, with personalized anti-VEGF therapy for those at high risk of thrombosis.

Enhancing pharmacovigilance and regulatory updates

As knowledge of faricimab-related AEs continues to evolve, increased pharmacovigilance is necessary to ensure patient safety. It is recommended that newly identified AEs, such as macular ischemia, optic nerve injury, and keratic precipitates, be incorporated into updated drug labeling to enhance physician awareness.

Furthermore, AE incidence patterns appear to vary across ethnic groups. Asian patients show a higher risk of

retinal vascular events, whereas Western patients exhibit a stronger inflammatory AE signal. Therefore, refining ethnicity-specific treatment guidelines may improve safety. For instance, Asian patients may require closer monitoring of retinal vascular health, whereas Western patients may benefit from stricter screening for inflammatory responses.

Developing patient-specific AE prediction models and integrating AI-based risk assessment tools could further optimize treatment strategies and improve AE monitoring. In particular, high-risk patients, such as those with diabetes or retinal vascular disease, may benefit from more frequent follow-ups to facilitate early detection and intervention, thereby reducing the likelihood of severe complications.

Limitations

This study utilized the FAERS and JADER databases, both spontaneous reporting systems prone to information bias, missing data, and reporting delays. FAERS includes consumer-submitted reports, which broaden AE coverage but may lack clinical validation. In contrast, JADER consists mainly of healthcare institution reports, ensuring higher data quality but a smaller sample size, which may limit the detection of rare AEs [44, 45]. Additionally, neither database includes detailed clinical background information (e.g., comorbidities, concomitant medications), restricting control over confounders and potentially leading to over- or underestimation of certain AE signals.

Disproportionality analysis using reporting odds ratio (ROR) is useful for signal detection but cannot establish causality and may generate false positives or negatives ["Abstracts of the 25th International Conference on Pharmacoepidemiology & Therapeutic Risk Management. Providence, Rhode Island, USA. August 16–19, 2009" 46, 47]. Rare AEs may be underestimated due to limited reports, while common ocular discomfort could be overestimated due to reporting bias. To address these limitations, this study cross-validated FAERS and JADER data, conducted subgroup analyses (sex and age) to reduce confounding effects, and applied multiple signal detection algorithms (ROR, PRR, IC) to improve reliability. Additionally, AEs closely related to underlying diseases were excluded to enhance specificity in faricimab-related AE detection.

It should also be noted that spontaneous reporting systems, such as FAERS and JADER, are prone to several biases that could impact the accuracy and reliability of the findings. One of the most significant limitations is underreporting, where adverse events (AEs) may be reported less frequently due to healthcare provider oversight or patients not reporting symptoms. Furthermore, the lack of denominator data in these databases means that the true incidence of AEs cannot be accurately determined, as the total number of patients exposed to the drug is unknown. Additionally, confounding by indication is another critical issue; patients with certain conditions are more likely to be prescribed specific drugs, which could influence the occurrence of AEs in ways that are not fully captured by the data.

These biases highlight the inherent limitations of relying solely on spontaneous reporting data and emphasize the need for more rigorous, controlled studies to validate the findings and mitigate potential sources of error. Additionally, the absence of validation through real-world clinical data should be acknowledged as a significant limitation. Future research should aim to integrate these findings with electronic health records or patient registries to enhance the accuracy and generalizability of the results.

Future research directions

While this study provides a comprehensive analysis of faricimab-related AEs, further research is needed to validate these findings in clinical settings. Integrating real-world data (RWD) from sources like electronic health records (EHRs) and insurance claims databases could enhance AE assessments by providing richer patient background information and long-term follow-up data. Compared to spontaneous reporting systems, RWD allows for a more comprehensive evaluation of safety profiles and AE risk factors [48, 49].

Machine learning and causal inference methods could further refine AE signal detection. Traditional disproportionality analysis relies on reporting frequencies, whereas machine learning can incorporate multidimensional patient data (e.g., medical history, concomitant medications) to develop more precise prediction models [50]. Techniques like Bayesian networks may help uncover causal relationships, while propensity score matching (PSM) can reduce baseline differences and improve AE association accuracy [51].

Additionally, prospective clinical studies, such as long-term observational cohorts or randomized controlled trials (RCTs), are needed to confirm AE patterns, identify high-risk populations, and validate new safety signals [52]. Biomarker research could further personalize AE monitoring and optimize the clinical use of faricimab, improving both safety and treatment outcomes.

Conclusion

Our study comprehensively analyzed the adverse events (AEs) associated with faricimab using the FAERS and JADER databases. At the system organ class (SOC) level, faricimab was primarily associated with eye disorders, general disorders and administration site conditions, and injury, poisoning, and procedural complications. At the

preferred term (PT) level, newly identified AEs included keratic precipitates, visual field defects, macular holes, epiretinal membranes, macular ischemia, optic nerve injury, and optic disc disorders. Although these AEs are rare, they warrant close clinical monitoring, particularly during long-term treatment.

By leveraging dual-database validation and subgroup analysis, this study provides a more comprehensive and regionally diverse safety assessment of faricimab. The findings highlight the need for individualized patient monitoring, particularly in populations with a higher risk of inflammatory or vascular AEs. While faricimab's dual-target mechanism remains a promising therapeutic strategy for ocular diseases, ongoing pharmacovigilance and real-world data integration are essential to further optimize its safety profile.

In conclusion, this study underscores the importance of proactive AE monitoring to maximize faricimab's therapeutic benefits while minimizing potential risks. Future research should focus on prospective validation of these AE signals and refinement of individualized treatment strategies to ensure optimal patient safety and clinical outcomes.

Supplementary information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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This study was conducted utilizing the FDA Adverse Event Reporting System (FAERS) database and the Japanese Adverse Drug Event Report (JADER). It is important to note that the information, outcomes, or interpretations presented in the study do not reflect any official position or opinion of the FDA or the PMDA. Moreover, we would like to thank everyone who participated in this study.

Author contributions

Chuanya Liu：Writing—original draft, Writing—review & editing, Methodology, Conceptualization; Shangze Li：Writing—original draft, Methodology, Data curation, Visualization; Ziyi Wang：Writing—review& editing, Formal analysis; Zhifu Li：Writing—review& editing, Visualization; Zhou Fang：Writing—review& editing, Visualization; Yuan Zhang：Writing—review & editing, Supervision; Yu Gao：Writing—review & editing, Supervision, Conceptualization.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

This study did not utilize individual-level data. Therefore, no new ethical approval from an ethics review committee was required.

Consent to participate

Not applicable.

competing interests

The authors declare no competing interests.

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