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Post-Marketing Safety Surveillance of Posaconazole: A Real-World Pharmacovigilance Study Utilizing the FDA Adverse Event Reporting System

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Research Article

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Abstract

Objective

To systematically evaluate post-marketing adverse event (AE) signals and their time-to-onset patterns of posaconazole using real-world data from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS), thereby providing reference for clinical medication safety.

Methods

FAERS data from Q1 2006 to Q2 2026 were extracted. Reports listing posaconazole as the primary suspect drug were included. Disproportionality analysis was performed using four algorithms: reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and empirical Bayesian geometric mean (EBGM) based on the multi-item gamma Poisson shrinker (MGPS). Time-to-onset (TTO) characteristics were assessed using the Weibull shape parameter test.

Results

A total of 2,542 reports involving 6,031 AE cases were included. At the system organ class (SOC) level, the top three strongest signals were endocrine disorders (ROR = 4.30), hepatobiliary disorders (ROR = 3.76), and blood and lymphatic system disorders (ROR = 1.68). At the preferred term (PT) level, 67 significant signals meeting all four algorithm criteria were detected, of which 35 were novel signals not documented in the package insert. The strongest signals included pseudoaldosteronism (ROR = 1968.76), acquired apparent mineralocorticoid excess (ROR = 2092.35), antibiotic level below therapeutic (ROR = 4085.81), and anticoagulation drug level increased (ROR = 502.99). The median TTO was 12 days (interquartile range: 4–35 days), with 71.56% of AEs occurring within the first 30 days of treatment. The Weibull shape parameter β was 0.656 (95% CI: 0.611–0.700), indicating a decreasing AE risk over time.

Conclusion

Our pharmacovigilance analysis of real-world FAERS data reveals safety signals associated with posaconazole use. The early treatment period, particularly the first month, shows the highest AE risk, which declines over time. Clinicians should enhance monitoring of liver function, serum potassium, blood pressure, and ECG within the first 30 days, and remain vigilant for CYP3A4-mediated drug interactions, especially with anticoagulants and immunosuppressants.

1 Introduction

Posaconazole is a second-generation broad-spectrum triazole antifungal agent that exerts its antifungal activity by inhibiting lanosterol 14α-demethylase (CYP51), a key enzyme in ergosterol biosynthesis(Alsulaimany et al. 2025; Kauffman et al. 2007). Posaconazole was first approved by the U.S. Food and Drug Administration (FDA) in 2006 for the prophylaxis of invasive Aspergillus and Candida infections in severely immunocompromised patients, including those with hematological malignancies, graft-versus-host disease (GVHD) following

allogeneic hematopoietic stem cell transplantation, and prolonged neutropenia(Pappas et al. 2009; Ullmann et al. 2007). Over the past two decades, the clinical application of posaconazole has expanded considerably. The introduction of intravenous and delayed-release tablet formulations has improved bioavailability and facilitated use in patients unable to tolerate the oral suspension(Chen et al. 2020). It has also been approved for the treatment of oropharyngeal candidiasis, including cases refractory to itraconazole and/or fluconazole(Nagappan and Deresinski 2007).

With the widespread clinical use of posaconazole, its safety profile has garnered increasing attention. Previous clinical trials have identified common adverse events associated with posaconazole, such as gastrointestinal reactions, liver function abnormalities, and rash(Maertens et al. 2021; Yang et al. 2024). However, clinical trials are constrained by limited sample sizes, short follow-up durations, and strict inclusion/exclusion criteria, which preclude a complete reflection of the safety profile in the real-world broad patient population. Moreover, rare and delayed adverse events that may emerge during long-term post-marketing use require continuous monitoring and mining through large-scale real-world data. The FDA Adverse Event Reporting System (FAERS) is one of the largest spontaneous adverse event reporting databases globally and serves as a core data source for post-marketing pharmacovigilance research([CSL STYLE ERROR: reference with no printed form.]). In-depth mining of FAERS data enables comprehensive characterization of a drug's AE profile, identification of potential risk signals, and elucidation of AE occurrence patterns, thereby providing essential evidence for clinical medication safety(Dai et al. 2026).

This study aims to conduct a comprehensive pharmacovigilance analysis of posaconazole-associated adverse events using real-world FAERS data with multiple signal mining algorithms, systematically characterizing the distribution features, signal intensities, and time-to-onset patterns to uncover potential safety risks and inform rational clinical use of posaconazole.

2. Methods

2.1. Study Design and Data Source

This retrospective pharmacovigilance study utilized data from the FAERS database maintained by the U.S. Food and Drug Administration. FAERS is a spontaneous reporting system that collects AE reports from healthcare professionals, consumers, and manufacturers in the United States and globally([CSL STYLE ERROR: reference with no printed form.]). Publicly available FAERS data files from Q1 2006 to Q2 2026 were downloaded from the FDA website. The database comprises seven datasets: demographic information (DEMO), drug information (DRUG), adverse events (REAC), outcomes (OUTC), indications (INDI), therapy start and end dates (THER), and report sources (RPSR) [18]. Reports related to posaconazole were extracted using the generic drug name "posaconazole." All preferred terms (PTs) were mapped to corresponding system organ classes (SOCs) according to the Medical Dictionary for Regulatory Activities (MedDRA) version 28.1. For terminology consistency, earlier versions were programmatically aligned with this version. Duplicate entries were removed based on unique report identifiers (primaryid). Only reports in which posaconazole was designated as the primary suspect (PS) drug (role_cod = 'PS') were included to minimize confounding from concomitant medications (see Fig. 1 for detailed flowchart).

This study did not require ethical approval or informed consent, as it only utilized publicly available, anonymized AE data from the FAERS database without introducing new personal data or interventions. The study complies with the ethical principles of the Declaration of Helsinki.

2.2. Time-to-Onset (TTO) Analysis of Posaconazole-Associated AEs

TTO was calculated as EVENT_DT minus START_DT, with a minimum value of 1 day assigned to events occurring on the start date(Shu et al. 2023). Only reports with available TTO data were analyzed. Reports with inaccurate, missing, or erroneous data (e.g., negative TTO values, event dates preceding drug start dates) were excluded to ensure TTO accuracy.

The incidence of AEs changes over time following treatment initiation. The Weibull shape parameter (WSP) test was employed for TTO analysis to characterize the increasing or decreasing risk of AE occurrence over time(Han et al. 2026). The Weibull distribution is defined by two parameters: the scale parameter (α) and the shape parameter (β). The scale parameter α determines the scale of the distribution function, while the shape parameter β determines its shape. The WSP test describes three risk types: early failure type, where AE risk decreases over time (β < 1 and 95% confidence interval [CI] < 1); random failure type, where AE risk remains constant over time (β equals or approximates 1, with 95% CI containing 1); and wear-out failure type, where AE risk increases over time (β > 1 and 95% CI > 1).

2.3. Statistical Analysis

Four well-established algorithms were used for disproportionality analysis: reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and empirical Bayesian geometric mean (EBGM) based on the multi-item gamma Poisson shrinker (MGPS). Signal detection thresholds were as follows: lower bound of 95% CI for ROR > 1 with report count ≥ 3; PRR ≥ 2 with $\chi^2 \geq 4$ and report count ≥ 3; lower bound of 95% CI for information component (IC025) of BCPNN > 0; and lower bound of 95% CI for EBGM (EBGM05) ≥ 2. Corresponding formulas and thresholds are provided in Supplementary Table S1. Signals were defined as statistically significant associations identified by these methods. Potential novel signals were identified as significant PTs not listed or prominently highlighted in the approved prescribing information (the novelty signals are identified as any significant AE which was not listed in package inserts(Yin et al. 2022). Given the exploratory nature of this pharmacovigilance study, we did not adjust for multiple comparisons, consistent with the standard practice in FAERS-based disproportionality analyses, where signals are considered hypothesis-generating. All statistical analysis was conducted using R version 4.4.1 software.

3 Results

3.1 Descriptive Analysis

A total of 24,812,425 case reports were collected in the FAERS database spanning from Q1 2006 to Q2 2026. After removing 4,121,528 duplicate reports, 20,690,897 deduplicated case reports remained. Among these, 2,542 AE reports identified posaconazole as the PS drug, encompassing 6,031 adverse event reports (AERs).

In terms of gender, there were 1,277 male cases (50.24%), 906 female cases (35.64%), and 359 cases (14.12%) with missing gender information. Regarding age distribution, 236 cases (9.28%) were under 18 years, 971 cases

(38.20%) were between 18 and 65 years, 586 cases (23.05%) were 65 years or older, and 749 cases (29.46%) had unknown age. The majority of patients received posaconazole via the oral route (n = 1,916, 75.37%), followed by intravenous administration (n = 135, 5.31%). In terms of report sources, physicians were the largest reporter group (n = 782, 30.76%), followed by consumers (n = 586, 23.05%), health professionals (n = 491, 19.32%), and pharmacists (n = 253, 9.95%).

Regarding clinical outcomes, death was reported in 407 cases (16.01%), hospitalization or prolongation of hospitalization in 428 cases (16.84%), other serious events in 368 cases (14.48%), life-threatening events in 69 cases (2.71%), and disability in 18 cases (0.71%). The outcome was unknown in 1,252 cases (49.25%). The detailed clinical characteristics are summarized in Table 1.

Table 1
Clinical characteristics of reports with posaconazole from the FAERS database (the first quarter of 2006 to the second quarter of 2026).

Characteristics	Case number, n	Case proportion, %
Sex		
Female	906	35.64
Male	1277	50.24
Unknown	359	14.12
Age(years)		
< 18	236	9.28
18 ~ 65	971	38.20
≥ 65	586	23.05
Unknown	749	29.46
Weight(kg)		
< 50	127	5.00
50 ~ 100	323	12.71
≥ 100	19	0.75
Unknown	2073	81.55
Reporter		
Physician	782	30.76
Health-professional	491	19.32
Pharmacist	253	9.95
Unknown	430	16.92
Consumer	586	23.05
Route of administration		
Oral	1916	75.37
Intravenous	135	5.31
Other	7	0.28
Unknown	484	19.04
Outcomes of adverse events		
Death	407	16.01
Disability	18	0.71

Characteristics	Case number, n	Case proportion, %
Sex		
Hospitalization	428	16.84
Life-Threatening	69	2.71
Other Serious	368	14.48
Unknown	1252	49.25

3.2 Signal Detection of Posaconazole at the System Organ Class Level

The study indicates that 6,031 AERs induced by posaconazole occurred across 27 organ systems. The most common systems were injury, poisoning and procedural complications (n = 1,164, ROR 1.99, PRR 1.80, IC 0.85, EBGM 1.80), general disorders and administration site conditions (n = 1,067, ROR 1.02, PRR 1.02, IC 0.02, EBGM 1.02), and investigations (n = 568, ROR 1.61, PRR 1.55, IC 0.64, EBGM 1.55). Other frequently reported SOCs included infections and infestations (n = 485), gastrointestinal disorders (n = 403), and nervous system disorders (n = 251).

Notably, according to the ROR level, the top three SOCs with the strongest posaconazole-associated AE signals were endocrine disorders [ROR 4.30 (3.38–5.47)], hepatobiliary disorders [ROR 3.76 (3.27–4.32)], and blood and lymphatic system disorders [ROR 1.68 (1.44–1.96)], indicating a strong statistical association between posaconazole and these organ system toxicities. The details of all SOC-level signals are presented in Table 2.

Table 2
Signal strength of AEs of posaconazole at the SOC level in FAERS database.

System organ class (SOC)	N	ROR (95%CI)	PRR((χ²)	IC(IC025)	EBGM(EBGM05)
Injury, poisoning and procedural complications	1164	1.99 (1.87–2.12)	1.8 (464.22)	0.85 (0.75)	1.8 (1.69)
General disorders and administration site conditions	1067	1.02 (0.96–1.09)	1.02 (0.36)	0.02 (-0.07)	1.02 (0.95)
Investigations	568	1.61 (1.48–1.76)	1.55 (119.37)	0.64 (0.51)	1.55 (1.43)
Infections and infestations	485	1.57 (1.43–1.72)	1.53 (92.71)	0.61 (0.47)	1.53 (1.39)
Gastrointestinal disorders	403	0.77 (0.69–0.85)	0.78 (26.16)	-0.35 (-0.5)	0.78 (0.71)
Nervous system disorders	251	0.48 (0.42–0.54)	0.5 (138.18)	-1 (-1.19)	0.5 (0.44)
Hepatobiliary disorders	206	3.76 (3.27–4.32)	3.67 (403.45)	1.87 (1.65)	3.67 (3.19)
Skin and subcutaneous tissue disorders	204	0.6 (0.52–0.69)	0.62 (51.58)	-0.7 (-0.9)	0.62 (0.54)
Respiratory, thoracic and mediastinal disorders	202	0.7 (0.61–0.81)	0.71 (24.5)	-0.49 (-0.69)	0.71 (0.62)
Cardiac disorders	178	1.16 (1–1.35)	1.16 (3.8)	0.21 (-0.01)	1.16 (1)
Blood and lymphatic system disorders	170	1.68 (1.44–1.96)	1.66 (45.7)	0.73 (0.5)	1.66 (1.43)
Metabolism and nutrition disorders	168	1.3 (1.11–1.51)	1.29 (11.01)	0.36 (0.14)	1.29 (1.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	128	0.83 (0.69–0.98)	0.83 (4.59)	-0.27 (-0.52)	0.83 (0.7)
Renal and urinary disorders	117	1.04 (0.87–1.25)	1.04 (0.2)	0.06 (-0.21)	1.04 (0.87)
Musculoskeletal and connective tissue disorders	116	0.36 (0.3–0.43)	0.37 (128.47)	-1.42 (-1.68)	0.37 (0.31)

AEs, adverse events; SOC, system organ class; FAERS, Food and Drug Administration Adverse Event Reporting System; ROR, reporting odds ratio; PRR, proportional reporting ratio; EBGM, empirical Bayesian geometric mean.

System organ class (SOC)	N	ROR (95%CI)	PRR((χ²)	IC(IC025)	EBGM(EBGM05)
Psychiatric disorders	110	0.32 (0.27–0.39)	0.33 (155.78)	-1.59 (-1.86)	0.33 (0.28)
Vascular disorders	101	0.79 (0.65–0.97)	0.8 (5.28)	-0.33 (-0.61)	0.8 (0.66)
Surgical and medical procedures	84	1 (0.81–1.24)	1 (0)	0 (-0.32)	1 (0.81)
Immune system disorders	76	1.13 (0.9–1.42)	1.13 (1.12)	0.17 (-0.16)	1.13 (0.9)
Endocrine disorders	67	4.3 (3.38–5.47)	4.26 (167.68)	2.09 (1.67)	4.26 (3.35)
Product issues	60	0.58 (0.45–0.74)	0.58 (18.57)	-0.79 (1.15)	0.58 (0.45)
Eye disorders	57	0.46 (0.35–0.6)	0.47 (35.72)	-1.1 (-1.47)	0.47 (0.36)
Ear and labyrinth disorders	15	0.58 (0.35–0.96)	0.58 (4.6)	-0.79 (-1.47)	0.58 (0.35)
Congenital, familial and genetic disorders	13	0.73 (0.43–1.26)	0.73 (1.25)	-0.45 (-1.19)	0.73 (0.43)
Reproductive system and breast disorders	9	0.17 (0.09–0.33)	0.17 (36.18)	-2.54 (-3.33)	0.17 (0.09)
Social circumstances	8	0.28 (0.14–0.56)	0.28 (14.89)	-1.84 (-2.68)	0.28 (0.14)
Pregnancy, puerperium and perinatal conditions	4	0.16 (0.06–0.42)	0.16 (17.82)	-2.65 (-3.68)	0.16 (0.06)

AEs, adverse events; SOC, system organ class; FAERS, Food and Drug Administration Adverse Event Reporting System; ROR, reporting odds ratio; PRR, proportional reporting ratio; EBGM, empirical Bayesian geometric mean.

3.3 Signal Detection of Posaconazole at the Preferred Term Level

A total of 404 types of PTs with reporting counts ≥ 3 were reported across different organ systems (Supplementary Table S2). We examined PT signals using four algorithms simultaneously, and a total of 67 significant disproportionality PTs met the criteria of all four algorithms (Supplementary Table S3). Among these, 32 PTs with significant disproportionation appeared in the drug label or clinical trial and post-marketing results. We listed the top 20 PTs, as shown in Table 3. The top three AEs with the strongest signals were acquired apparent mineralocorticoid excess (n = 10, ROR 2092.35), pseudoaldosteronism (n = 31, ROR 1968.76), and

labelled drug-drug interaction issue (n = 37, ROR 282.46). Other notable signals included hepatocellular injury (n = 28, ROR 17.66), drug-induced liver injury (n = 32, ROR 10.82), hypokalaemia (n = 45, ROR 10.19), electrocardiogram QT prolonged (n = 31, ROR 8.81), and torsade de pointes (n = 6, ROR 7.90).

Table 3
The top 20 signal strength of adverse events that appear in the drug label or clinical trials/post-marketing experience of posaconazole at the preferred term (PT) level that fit four algorithms simultaneously.

System organ class (SOC)	PTs	N	ROR (95%CI)	PRR(χ^2)	IC(IC025)	EBGM(EBGM05)
Endocrine disorders	Acquired apparent mineralocorticoid excess	10	2092.35 (1059.4–4132.47)	2088.88 (17331.75)	10.76 (2.5)	1735 (878.47)
Endocrine disorders	Pseudoaldosteronism	31	1968.76 (1339.56–2893.52)	1958.65 (50913.61)	10.68 (4.42)	1644.21 (1118.73)
Injury, poisoning and procedural complications	Labelled drug-drug interaction issue	37	282.46 (203.56–391.95)	280.74 (10038.31)	8.09 (4.59)	273.27 (196.93)
Endocrine disorders	Primary adrenal insufficiency	5	177.85 (73.44–430.69)	177.7 (863.54)	7.45 (1.35)	174.68 (72.13)
General disorders and administration site conditions	Inhibitory drug interaction	9	55.81 (28.97–107.51)	55.73 (481.11)	5.79 (2.19)	55.43 (28.78)
Investigations	Blood bilirubin unconjugated increased	3	42.97 (13.82–133.58)	42.95 (122.4)	5.42 (0.45)	42.77 (13.76)
Cardiac disorders	Arrhythmia supraventricular	3	27.85 (8.97–86.52)	27.84 (77.42)	4.8 (0.41)	27.77 (8.94)
Investigations	Drug level decreased	19	19.35 (12.33–30.38)	19.3 (329.06)	4.27 (2.68)	19.26 (12.27)
Hepatobiliary disorders	Hepatocellular injury	28	17.66 (12.18–25.61)	17.58 (437.3)	4.13 (2.94)	17.56 (12.11)
Investigations	Bilirubin conjugated increased	3	13.26 (4.27–41.15)	13.25 (33.94)	3.73 (0.26)	13.24 (4.26)
Hepatobiliary disorders	Cholestasis	22	11.97 (7.87–18.19)	11.93 (220.01)	3.57 (2.41)	11.91 (7.84)
Hepatobiliary disorders	Drug-induced liver injury	32	10.82 (7.64–15.32)	10.77 (283.36)	3.43 (2.55)	10.76 (7.6)
Metabolism and nutrition disorders	Hypokalaemia	45	10.19 (7.6–13.66)	10.12 (369.78)	3.34 (2.65)	10.11 (7.54)

ROR, reporting odds ratio; PRR, proportional reporting ratio; EBGM, empirical Bayesian geometric mean; SOC, system organ class; PT, preferred term.

System organ class (SOC)	PTs	N	ROR (95%CI)	PRR(χ^2)	IC(IC025)	EBGM(EBGM05)
Hepatobiliary disorders	Hyperbilirubinaemia	10	10.06 (5.41–18.7)	10.04 (81.34)	3.33 (1.59)	10.03 (5.39)
Hepatobiliary disorders	Hepatotoxicity	20	9.38 (6.05–14.56)	9.35 (149.15)	3.22 (2.11)	9.35 (6.02)
Investigations	Electrocardiogram qt prolonged	31	8.81 (6.19–12.53)	8.77 (213.22)	3.13 (2.31)	8.76 (6.15)
General disorders and administration site conditions	Potentiating drug interaction	3	8.8 (2.84–27.31)	8.8 (20.72)	3.14 (0.13)	8.79 (2.83)
Cardiac disorders	Ventricular arrhythmia	3	8.46 (2.73–26.26)	8.46 (19.72)	3.08 (0.12)	8.45 (2.72)
Metabolism and nutrition disorders	Hypomagnesaemia	11	8.22 (4.55–14.85)	8.21 (69.56)	3.04 (1.52)	8.2 (4.54)
Cardiac disorders	Torsade de pointes	6	7.9 (3.55–17.61)	7.9 (36.12)	2.98 (0.9)	7.89 (3.54)

ROR, reporting odds ratio; PRR, proportional reporting ratio; EBGM, empirical Bayesian geometric mean; SOC, system organ class; PT, preferred term.

In particular, our study identified 35 unexpected and significant disproportionate signals that were not mentioned in posaconazole's instructions (Table 4). The most intense unexpected signals were noted for antibiotic level below therapeutic (n = 29, ROR 4085.81, PRR 4066.17, IC 11.51, EBGM 2910.38), anticoagulation drug level increased (n = 15, ROR 502.99, PRR 501.74, IC 8.90, EBGM 478.34), and drug level below therapeutic (n = 67, ROR 129.49, PRR 128.06, IC 6.98, EBGM 126.49). Other noteworthy unexpected signals included blood uric acid decreased (n = 3, ROR 63.47), capillary leak syndrome (n = 3, ROR 15.16), and various opportunistic infections such as enterococcal bacteraemia, adenovirus infection, BK virus infection, and cytomegalovirus infection.

Table 4
Signal strength of adverse events that are unexpected findings of posaconazole-related AEs (N = 35) at the preferred term (PT) level that fit four algorithms simultaneously.

System Organ Class (SOC)	Preferred terms (PT)	N	ROR (95%CI)	PRR(χ^2)	IC(IC025)	EBGM(EBGM05)
Investigations	Antibiotic level below therapeutic	29	4085.81 (2655.28–6287.02)	4066.17 (84351.52)	11.51 (4.29)	2910.38 (1891.4)
Investigations	Anticoagulation drug level increased	15	502.99 (299.35–845.15)	501.74 (7145.9)	8.9 (3.22)	478.34 (284.69)
Investigations	Drug level below therapeutic	67	129.49 (101.63–164.99)	128.06 (8343.13)	6.98 (5.12)	126.49 (99.28)
Investigations	Blood uric acid decreased	3	63.47 (20.39–197.56)	63.44 (183.24)	5.98 (0.48)	63.06 (20.26)
Surgical and medical procedures	Gastrointestinal tube insertion	8	33.36 (16.65–66.81)	33.31 (249.94)	5.05 (1.89)	33.21 (16.58)
Congenital, familial and genetic disorders	Congenital aplasia	7	31.81 (15.14–66.83)	31.77 (207.99)	4.99 (1.69)	31.68 (15.08)
Infections and infestations	Enterococcal bacteraemia	3	29.4 (9.46–91.33)	29.38 (82.02)	4.87 (0.41)	29.3 (9.43)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Differentiation syndrome	3	27.78 (8.94–86.28)	27.76 (77.19)	4.79 (0.41)	27.69 (8.91)
Vascular disorders	Capillary leak syndrome	3	15.16 (4.88–47.07)	15.16 (39.61)	3.92 (0.29)	15.14 (4.88)
Renal and urinary disorders	Renal tubular disorder	4	14.61 (5.48–38.95)	14.6 (50.59)	3.87 (0.68)	14.58 (5.47)
Infections and infestations	Adenovirus infection	4	14.49 (5.43–38.64)	14.48 (50.12)	3.85 (0.68)	14.46 (5.42)
Gastrointestinal disorders	Malabsorption	7	13.98 (6.66–29.34)	13.96 (84.12)	3.8 (1.39)	13.94 (6.64)

AEs, adverse events; ROR, reporting odds ratio; PRR, proportional reporting ratio; EBGM, empirical Bayesian geometric mean; SOC, system organ class; PT, preferred term.

System Organ Class (SOC)	Preferred terms (PT)	N	ROR (95%CI)	PRR(χ^2)	IC(IC025)	EBGM(EBGM05)
Gastrointestinal disorders	Ileus paralytic	6	13.93 (6.25–31.03)	13.91 (71.82)	3.8 (1.2)	13.9 (6.24)
Infections and infestations	Brain abscess	3	12.28 (3.96–38.12)	12.28 (31.04)	3.62 (0.24)	12.26 (3.95)
Investigations	Drug level increased	18	11.27 (7.1–17.91)	11.24 (167.85)	3.49 (2.2)	11.23 (7.07)
Metabolism and nutrition disorders	Hypophosphataemia	8	11.26 (5.63–22.54)	11.25 (74.65)	3.49 (1.43)	11.24 (5.62)
Nervous system disorders	Metabolic encephalopathy	3	10.31 (3.32–31.98)	10.3 (25.17)	3.36 (0.19)	10.29 (3.32)
Renal and urinary disorders	Azotaemia	4	10.26 (3.85–27.36)	10.25 (33.37)	3.36 (0.55)	10.24 (3.84)
Investigations	Immunosuppressant drug level increased	3	9.42 (3.04–29.23)	9.42 (22.55)	3.23 (0.16)	9.41 (3.03)
Infections and infestations	Bk virus infection	3	9.3 (3–28.85)	9.29 (22.19)	3.22 (0.15)	9.29 (2.99)
Investigations	Drug level above therapeutic	4	9.14 (3.43–24.38)	9.14 (28.96)	3.19 (0.51)	9.13 (3.42)
Skin and subcutaneous tissue disorders	Toxic skin eruption	8	8.19 (4.09–16.39)	8.18 (50.39)	3.03 (1.22)	8.18 (4.09)
Skin and subcutaneous tissue disorders	Dermatitis exfoliative	4	8.18 (3.07–21.81)	8.17 (25.17)	3.03 (0.46)	8.17 (3.06)
Eye disorders	Conjunctival haemorrhage	3	8.11 (2.61–25.16)	8.1 (18.67)	3.02 (0.1)	8.1 (2.61)
Nervous system disorders	Peripheral sensory neuropathy	4	7.08 (2.66–18.88)	7.08 (20.86)	2.82 (0.38)	7.07 (2.65)
Gastrointestinal disorders	Enteritis	4	6.12 (2.3–16.32)	6.12 (17.12)	2.61 (0.3)	6.12 (2.29)

AEs, adverse events; ROR, reporting odds ratio; PRR, proportional reporting ratio; EBGM, empirical Bayesian geometric mean; SOC, system organ class; PT, preferred term.

System Organ Class (SOC)	Preferred terms (PT)	N	ROR (95%CI)	PRR(χ^2)	IC(IC025)	EBGM(EBGM05)
Product issues	Product supply issue	4	5.89 (2.21–15.69)	5.88 (16.2)	2.56 (0.28)	5.88 (2.21)
Injury, poisoning and procedural complications	Product use issue	103	5.8 (4.77–7.05)	5.72 (401.89)	2.51 (2.17)	5.71 (4.7)
Cardiac disorders	Sinus bradycardia	5	5.31 (2.21–12.78)	5.31 (17.49)	2.41 (0.45)	5.31 (2.21)
Skin and subcutaneous tissue disorders	Drug eruption	9	5.29 (2.75–10.17)	5.28 (31.21)	2.4 (0.97)	5.28 (2.74)
Nervous system disorders	Polyneuropathy	6	5.22 (2.35–11.64)	5.22 (20.46)	2.38 (0.61)	5.22 (2.34)
Infections and infestations	Cytomegalovirus infection	8	4.98 (2.49–9.97)	4.98 (25.42)	2.31 (0.82)	4.98 (2.49)
Skin and subcutaneous tissue disorders	Petechiae	5	4.97 (2.07–11.94)	4.96 (15.81)	2.31 (0.4)	4.96 (2.06)
Infections and infestations	Clostridium difficile colitis	5	4.87 (2.02–11.7)	4.86 (15.33)	2.28 (0.39)	4.86 (2.02)
Skin and subcutaneous tissue disorders	Rash maculo-papular	9	4.21 (2.19–8.1)	4.21 (21.99)	2.07 (0.76)	4.2 (2.19)

AEs, adverse events; ROR, reporting odds ratio; PRR, proportional reporting ratio; EBGM, empirical Bayesian geometric mean; SOC, system organ class; PT, preferred term.

3.4 Time to Onset Analysis of Posaconazole-Associated AEs

The onset times of posaconazole-related AEs were extracted and analyzed from the FAERS database. Among the 2,542 case reports, 429 cases had available onset time data. The median onset time was approximately 12 days [interquartile range (IQR) 4–35 days]. The majority of the AEs occurred within 30 days (n = 307, 71.56%), followed by 31–60 days (n = 51, 11.89%), 61–90 days (n = 26, 6.06%), and 91–120 days (n = 14, 3.26%). Over 89% of the AEs occurred within 90 days (89.51%). Notably, data showed that AEs may still occur more than 360 days after posaconazole treatment, which accounted for 1.63% of all AEs with known onset times. The WSP analysis yielded a β value of 0.656 (95% CI: 0.611–0.700), with $\beta < 1$ indicating a decreasing hazard function over time. The onset times of AEs for posaconazole are described in Fig. 2.

4 Discussion

Continuous attention to the risk signals of adverse drug reactions after marketing is essential for evaluating drug safety and maintaining the balance of benefits and risks in clinical practice. This study provided a comprehensive description of post-marketing adverse event reports in patients receiving posaconazole from the FAERS database using four statistical procedures (ROR, PRR, BCPNN, and MGPS). To our knowledge, this study represents one of the most comprehensive pharmacovigilance analyses specifically dedicated to posaconazole, covering a 20-year period from 2006 to 2026.

Our findings revealed that posaconazole-associated adverse events occurred more frequently in males (50.24%) than in females (35.64%). This gender distribution likely reflects the characteristics of the underlying patient population, as posaconazole is primarily used for prophylaxis and treatment in high-risk groups for invasive fungal infections, such as patients with hematological malignancies and transplant recipients, where gender distribution may differ. Based on GLOBOCAN 2022 and Global Burden of Disease 2021 data, studies have demonstrated that the age-standardized incidence rates of hematological malignancies in males and females worldwide are 16.13/100,000 and 11.24/100,000, respectively(Lin et al. 2026); another study based on GLOBOCAN 2022 data reported a higher lifetime risk of hematological malignancies in males (1.79%) compared to females (1.54%)(Sun et al. 2025). Taking multiple myeloma (MM) as an example, epidemiological data indicate that the incidence in males accounts for approximately 57%, with females at 43%(Ansarian et al. 2025). A 2021 report on hematopoietic stem cell transplant recipients showed that among all transplanted patients, males accounted for 61.8%, while females accounted for only 38.2%(Eryilmaz-Eren et al. 2022). In both autologous transplantation (commonly used for myeloma) and allogeneic transplantation (commonly used for leukemia), the proportion of males significantly exceeds that of females(Eryilmaz-Eren et al. 2022).

Notably, in terms of reporting sources, physicians and consumers ranked as the top two reporters. This dual attention from both professional and public domains further underscores the practical necessity of this study—timely and systematic evaluation of the drug's safety profile is of direct policy and practical significance for guiding rational clinical use and protecting public health.

According to the disproportionality analysis, many organs or tissues may be affected. Our study showed that at the SOC level, the most frequently reported significant signals were injury, poisoning and procedural complications (n = 1164), general disorders and administration site conditions (n = 1067), and investigations (n = 568). Among these, the major significant adverse events included pyrexia, nausea, diarrhoea, vomiting, cough, hypertension, and blood potassium decreased. These results are consistent with the package insert and clinical trial data(Cornely et al. 2017; Hachem et al. 2008; Kang et al. 2026).

At the SOC level, disproportionality signals indicated that the endocrine system faced the strongest risk. Notably, pseudoaldosteronism and acquired apparent mineralocorticoid excess were the strongest PT-level signals among all labelled adverse events. Studies have shown that posaconazole can induce pseudoaldosteronism and acquired apparent mineralocorticoid excess by inhibiting 11β-HSD2 and suppressing CYP11B1/CYP11B2, with hypertension, hypokalemia, and related symptoms reversible upon discontinuation or dose reduction(Agarwal et al. 2020; Beck et al. 2020; Thompson et al. 2019). The package insert also notes that posaconazole may cause pseudoaldosteronism, manifested as hypertension (new-onset or worsening) and laboratory abnormalities (hypokalemia, low renin and aldosterone, elevated 11-deoxycortisol). Blood pressure and serum potassium levels should be monitored, and if necessary, posaconazole should be discontinued, replaced with an antifungal agent that does not cause pseudoaldosteronism, or an aldosterone receptor antagonist should be used.

On the other hand, the risk of hepatobiliary disorders also warrants attention. At the PT level, significant signals included hepatocellular injury (n = 28, ROR 17.66), cholestasis (n = 22, ROR 11.97), drug-induced liver injury (n = 32, ROR 10.82), hyperbilirubinaemia (n = 10, ROR 10.06), and hepatotoxicity (n = 20, ROR 9.38). A single-center retrospective cohort study published in 2026 involving patients with hematological malignancies or those undergoing hematopoietic stem cell transplantation showed that among 100 patients receiving posaconazole prophylaxis, the incidence of hepatotoxicity was 7%. All hepatotoxicity events in that study were also assessed as mild(Steele et al. 2026). Another single-center retrospective cohort study analyzing the safety and efficacy of posaconazole delayed-release tablets versus oral suspension found that the overall incidence of hepatic dysfunction was 20.8% (30/144). The posaconazole prescribing information recommends monitoring liver function at baseline and during treatment([CSL STYLE ERROR: reference with no printed form.]). Elevations in liver function tests are generally reversible upon discontinuation.

It is noteworthy that studies have shown posaconazole-induced endocrine-related adverse effects are associated with high posaconazole plasma concentrations(Beck et al. 2020; Davis et al. 2020; Tantiprawan et al. 2021), whereas hepatobiliary system-related adverse effects have not been correlated with posaconazole plasma concentrations(Jia et al. 2020; Nickless et al. 2019; Pettit et al. 2017; Sabatino et al. 2023).

However, as a potent inhibitor of CYP3A4, posaconazole significantly elevates the plasma concentrations of many drugs metabolized by this enzyme, such as tacrolimus, cyclosporine, and certain statins. This drug-drug interaction is an important and modifiable factor contributing to increased risk of hepatic injury, and its risk may sometimes be even higher than that of the drug itself.

Additionally, although no overall elevated risk was observed at the cardiac SOC level, certain PTs, such as electrocardiogram QT prolonged (n = 31, ROR 8.81), torsade de pointes (n = 6, ROR 7.90), supraventricular arrhythmia (n = 3, ROR 27.85), and ventricular arrhythmia (n = 3, ROR 8.46), all met the criteria of the four algorithms simultaneously. Cases of QT interval prolongation and torsade de pointes leading to cardiac arrest have been reported in patients taking posaconazole(Eiden et al. 2007; Panos et al. 2016). Given the life-threatening nature of torsade de pointes, clinicians should exercise caution when using posaconazole in patients predisposed to arrhythmias and should avoid concomitant use with drugs known to prolong the QT interval. It is recommended to implement cardiac monitoring measures, such as electrocardiography, prior to posaconazole administration.

In this study, we identified numerous associations between posaconazole and systemic adverse events through pharmacovigilance analysis. However, due to strict enrollment criteria, small sample sizes, and short follow-up durations, clinical trials cannot provide reliable conclusions regarding rare and potential adverse events(Arrieta et al. 2019; Cornely et al. 2007; Kang et al. 2026; Wong et al. 2020). Based on our analysis, beyond the common AEs listed in the package insert, we focused on signals classified as strong signals in posaconazole-associated AE reports (Table 4).

Notably, these high-signal events, such as antibiotic level below therapeutic (n = 29, ROR 4085.81), anticoagulation drug level increased (n = 15, ROR 502.99), drug level below therapeutic (n = 67, ROR 129.49), and immunosuppressant drug level increased (n = 3, ROR 9.42), highlight the complexity and clinical significance of drug-drug interactions involving posaconazole. Posaconazole is a potent CYP3A4 inhibitor and a substrate of P-glycoprotein, positioning it at the center of numerous clinically significant drug interactions(Nagappan and Deresinski 2007; Nivoix et al. 2008).

Beyond the package insert's explicit contraindication of concomitant use with sirolimus due to an approximately 9-fold increase in sirolimus plasma concentrations, and the requirement for dose reduction and therapeutic drug monitoring of tacrolimus and cyclosporine(Gu et al. 2022), we are concerned about the strong signal of elevated anticoagulant drug levels, as posaconazole can increase the plasma concentrations of warfarin and other anticoagulants metabolized by CYP3A4, potentially leading to bleeding complications. A 2025 retrospective study published in *Clinical Transplantation* focusing on cardiothoracic transplant recipients observed that among patients concurrently taking posaconazole and apixaban, despite dose reduction of apixaban, two major bleeding events were still observed. The study also directly noted that posaconazole, through potent inhibition of CYP3A4, affects the exposure levels of anticoagulant drugs that are its substrates, such as apixaban(Concannon et al. 2025). These findings underscore the critical need for comprehensive medication reconciliation and therapeutic drug monitoring when prescribing posaconazole, particularly in transplant and hematology patients who frequently receive multiple concomitant medications.

Unexpected signals in the nervous system included metabolic encephalopathy, peripheral sensory neuropathy, and polyneuropathy. The official prescribing information for posaconazole explicitly warns that concomitant use with vinca alkaloids such as vincristine may cause severe adverse reactions including neurotoxicity, and lists peripheral neuropathy as a serious adverse reaction requiring vigilance([CSL STYLE ERROR: reference with no printed form.]). The possible mechanism is that posaconazole enhances the neurotoxicity of vincristine by inhibiting CYP3A4. Recent literature has also reported that posaconazole alone may cause peripheral neuropathy(Baxter et al. 2011; Hussain et al. 2019). Additionally, in canine models, posaconazole has been shown to induce neuronal phospholipidosis, particularly in the dorsal root ganglia where the blood-nerve barrier is relatively thin, consistent with the site of peripheral neuropathy and possibly representing an underlying mechanism of posaconazole neurotoxicity(Cartwright et al. 2009).

At the SOC level of infections and infestations, observed PTs with significant signals, including enterococcal bacteraemia, adenovirus infection, BK virus infection, cytomegalovirus infection, brain abscess, and Clostridioides difficile colitis, require cautious interpretation. Posaconazole is an antifungal agent used for the prophylaxis and treatment of fungal infections. Patients receiving posaconazole are typically severely immunocompromised (e.g., hematopoietic stem cell transplant recipients, patients with acute leukemia undergoing chemotherapy) and are inherently at high risk for various opportunistic infections(Balducci et al. 1983; Mehta and Langston 2009). These signals likely reflect the immunocompromised host status rather than drug-induced immunosuppression, but they underscore the importance of infection surveillance in this population.

Furthermore, unexpected signals related to the skin included toxic eruption, exfoliative dermatitis, drug eruption, and maculopapular rash. Although mild rash and pruritus are listed as common adverse reactions in the posaconazole package insert, signals of more severe skin reactions such as toxic eruption and exfoliative dermatitis alert clinicians to be vigilant about serious cutaneous reactions(Calogiuri et al. 2019), which may necessitate discontinuation of posaconazole.

Our findings showed that the median time to onset was approximately 12 days (IQR 4–35 days), with the majority of cases occurring within the first month (71.56%) and nearly 90% within the first 3 months. The WSP test yielded a β value of 0.656 (95% CI: 0.611–0.700), confirming that the risk of adverse reactions gradually decreases over time. These results clearly indicate that the highest risk period is the initial phase of

administration. This finding has important clinical implications: during the first month of posaconazole therapy, enhanced monitoring of liver function, serum electrolytes (potassium, magnesium), blood pressure, and electrocardiographic QT interval should be implemented.

Although the current study provides valuable insights into the safety profile of posaconazole, it is not without limitations. First, the FAERS database is a spontaneous reporting system subject to underreporting, missing reports, duplicate entries, and incomplete case information. The quality and completeness of reports vary considerably, and causality cannot be established based solely on spontaneous reports. Second, the lack of detailed data on underlying diseases, concomitant medications, dosing regimens, and patient comorbidities in the reports may confound signal detection results. Third, while this study confirmed statistical associations between posaconazole and certain adverse reactions, disproportionality signals do not represent population incidence rates or prove biological causality.

5 Conclusion

Our pharmacovigilance analysis of real-world FAERS data reveals safety signals associated with posaconazole use. The early treatment period, particularly the first month, shows the highest AE risk, which declines over time. Clinicians should enhance monitoring of liver function, serum potassium, blood pressure, and ECG within the first 30 days, and remain vigilant for CYP3A4-mediated drug interactions, especially with anticoagulants and immunosuppressants.

Declarations

Ethics approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication

Not applicable.

Competing interests

The authors declare no potential conflicts of interest.

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Author Contribution

Y.Y. conceptualized the study concept and design. Y.Y. and J.G. conducted research; Y.Y. analyzed the data; Y.Y. drafted the manuscript. J.G supervised the manuscript. All authors were involved in writing the paper and had final approval of the submitted and published versions.

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None

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article. The underlying datasets are available from the corresponding author on reasonable request.

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Figures

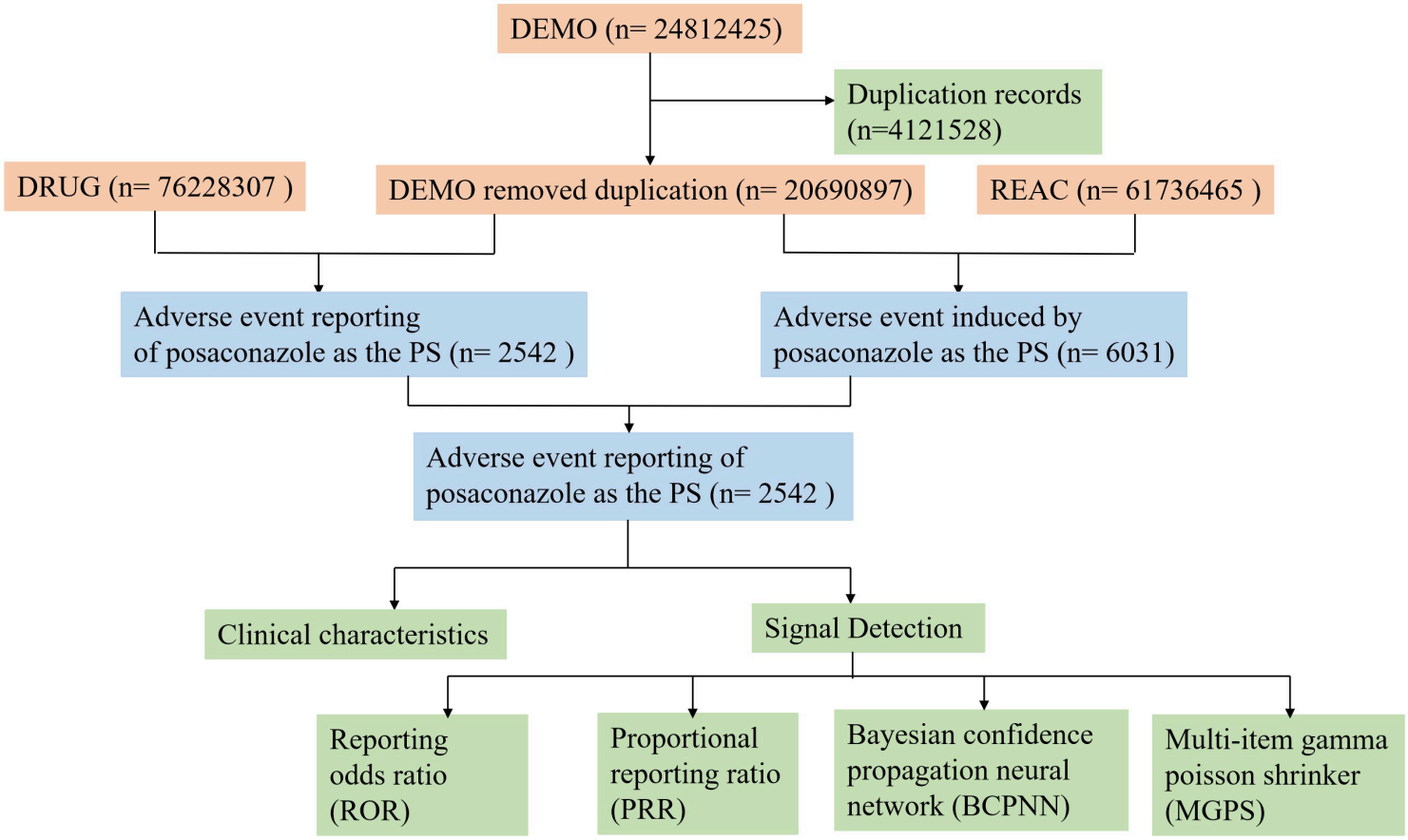

Figure 1

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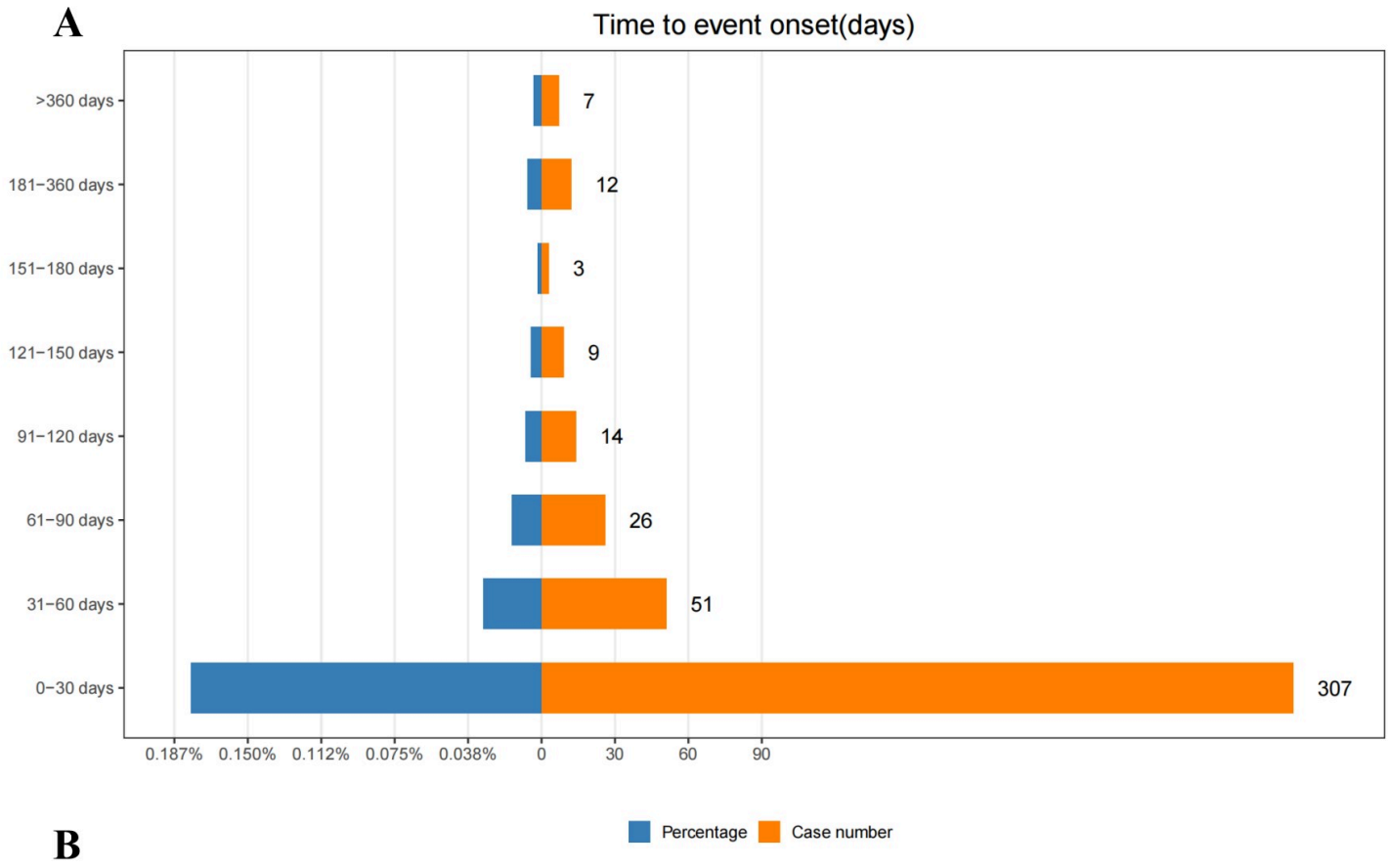

Drugs	TTO (Days)	Weibull distribution		Failure type
	Median (IQR)	Scale parameter: α (95% CI)	Shape parameter: β (95% CI)	
Posaconazole	12(4.0,35.0)	27.335(23.148,31.521)	0.656(0.611,0.700)	Early failure

Figure 2

Legend not included with this version

Supplementary Files

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