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Safety profile of artemether: Analysis based on 15-year data retrived from FDA adverse event reporting system (FAERS)

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ABSTRACT

Objective: Artemether is a semi-synthetic derivative of artemisinin and is widely used in the treatment of *Plasmodium* (*P.*) *falciparum* malaria. This study aimed to characterize the safety profile of artemether based on 15-year data retrived from FDA adverse event reporting system (FAERS).

Methods: This is a retrospective analysis on 15-year data of artemether-related adverse effects (AEs) retrieved from the FAERS. AEs were classified according to System Organ Class (SOC) and Preferred Terms (PT). Signal detection was performed using Reporting Odds Ratios (ROR), Proportional Reporting Ratios (PRR), and Empirical Bayes Geometric Mean (EBGM). Stratified analyses examined the impact of demographic factors such as sex, age, and time-to-onset. Temporal patterns and associated risk factors were also investigated.

Results: Haemolytic anaemia and haemolysis emerged as the most frequently reported AEs, exhibiting significantly elevated RORs (males: ROR 381.36, 95% *CI* 247.06–588.60; females: ROR 455.11, 95% *CI* 286.43–723.12). Sex-specific differences were evident, with females showing a higher incidence of reproductive-related AEs, including spontaneous abortion and premature labour. Temporal trend analysis revealed that the majority of AEs occurred within the first 30 days after the initiation of artemether administration, indicating a rapid onset. The most affected SOCs were blood and lymphatic system disorders and hepatobiliary disorders.

Conclusions: Artemether is associated with a notable frequency of early-onset AEs, particularly hematological and hepatobiliary disorders. The observed sex-specific vulnerability to reproductive AEs highlights the need for sex-conscious clinical approaches. Enhanced post-treatment monitoring and further investigations into the drug's pharmacokinetics and mechanistic pathways are recommended.

KEYWORDS: Artemether; Adverse events; FDA adverse event reporting system; Signal detection; Hematological toxicity; Hepatotoxicity

Summary

Question: What are the major adverse events associated with artemether based on long-term real-world pharmacovigilance data?

Findings: In this 15-year FAERS analysis, hematologic and hepatobiliary adverse events—particularly haemolytic anaemia and haemolysis—showed the highest reporting odds. Females demonstrated a higher risk of reproductive-related events, and most adverse events occurred within 30 days of artemether initiation.

Meaning: Artemether presents identifiable safety risks that warrant enhanced monitoring, especially for hematologic, hepatobiliary, and sex-specific adverse events.

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1. Introduction

Malaria remains a major global health burden, with over 263 million cases and nearly 600 000 deaths reported worldwide in 2023, primarily in sub-Saharan Africa[1]. Artemether, a semi-synthetic derivative of artemisinin developed from traditional Chinese medicine is widely used in the treatment of *Plasmodium (P.) falciparum* malaria because of its rapid action and favourable pharmacokinetics[2].

Although artemether is generally well tolerated, increasing reports of adverse effects (AEs) have raised concerns regarding its safety profile. Post-marketing surveillance systems such as the FDA adverse event reporting system (FAERS) offer valuable insights into the real-world risk associated with widely used pharmaceuticals. Disproportionality analysis of these datasets could reveal AE signals that may not be fully captured in pre-approval clinical trials.

This study aimed to characterize the nature, frequency, and risk factors of AEs associated with artemether, based on 15 years of FAERS data. We further examined demographic differences, temporal trends, and organ-specific toxicity patterns, with a focus on identifying safety signals requiring targeted clinical attention.

2. Methods

2.1. Data source and preprocessing

This study aimed to investigate AEs associated with artemether, particularly in the context of malaria treatment. Data were retrieved from the FAERS, a publicly accessible pharmacovigilance database that aggregates spontaneous reports from healthcare professionals, patients, and other stakeholders. The database contains detailed information on patient demographics, drug exposure, and AE details, all standardized using the Medical Dictionary for Regulatory Activities (MedDRA).

The target drug in this study was defined as artemether. Target adverse events (target AEs) included haemolytic anaemia, hepatocellular injury, jaundice, and Stevens-Johnson syndrome. Nontarget AEs were defined as all other AEs reported for artemether. These definitions were used throughout the analysis. AE records registered during 2010 and 2024 for which artemether was designated as the primary suspect drug were retrieved. The dataset underwent a series of preprocessing steps including deduplication, standardization, and categorization by System Organ Class (SOC) and Preferred Terms (PT). Rigorous data handling and quality assurance protocols were followed to ensure the validity and reliability of subsequent analyses.

2.2. Statistical analysis

All statistical analyses were conducted using R software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were used to summarize patient demographics and clinical characteristics. Signal detection was performed using disproportionality analysis, including Reporting Odds Ratios (ROR), Proportional Reporting Ratios (PRR), and Bayesian-based Empirical Bayes Geometric Mean (EBGM) are disproportionality analysis used to detect safety signals in pharmacovigilance. ROR and PRR assess the relative reporting frequency of adverse events, while EBGM provides a Bayesian adjustment for stability, reducing false positives. These metrics, summarized in Table 1, help to identify potential risks associated with artemether.

Numbers presented in tables and figures were reported at different analytical levels, including report-level, case-level, SOC-level, and PT-level. A single report or case may be involved with several SOCs or PTs, numbers at different levels are not mutually exclusive and therefore may not equal to the total number of reports (n=725) or cases (n=242). Subgroup and subset analyses further restricted counts to selected populations or signal-positive PTs, as specified in the corresponding table notes and figure legends.

Table 1. Formulas used for disproportionality analysis.

Method	Calculation formula	Positive signals
ROR	ROR= ad/bc, 95% *CI* of ROR=$e^{\ln ROR \pm 1.96}$	a≥3, 95% *CI*>1
PRR	PRR=[a/(a+b)]/[c/(c+d)], χ^2=[(adbc)^2 (a+b+c+d)]/[(a+b) (c+d) (a+c)(b+d)]	PRR≥2, χ^2≥4, a≥3
EBGM	EBGM = exp(μ + σZ)	EBGM≥ 2
IC	IC = $\log_2$(PRR) + adjustment term	IC> 0

Note: a, number of the target AE (haemolytic anaemia, hepatocellular injury, jaundice, *etc.*) by the target drug (artemether); b, number of nontarget AEs by artemether; c, number of target AEs by other drugs; d, number of nontarget AEs by other drugs. PRR: proportional reporting ratio; ROR: reported odds ratio; *CI*: Confidence interval. IC: Information component.

Temporal trends were assessed through time-to-onset (TTO) analysis, with AE occurrences categorized into predefined intervals (0-30, 31-60, 61-90, 91-120, 121-150, 151-180, 181-210, 211-240, 241-270, 271-300, 301-330, 331-360, and >360 days). Subgroup analysis stratified by age and sex were conducted using *Chi*-square tests for categorical comparisons and logistic regression models for Odds Ratio estimation. A two-sided *P*-value of <0.05 was considered statistically significant[3].

2.3. Reporting standards

This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and the standards set by the International Society of Pharmacovigilance (ISoP) for pharmacovigilance research. All reporting procedures

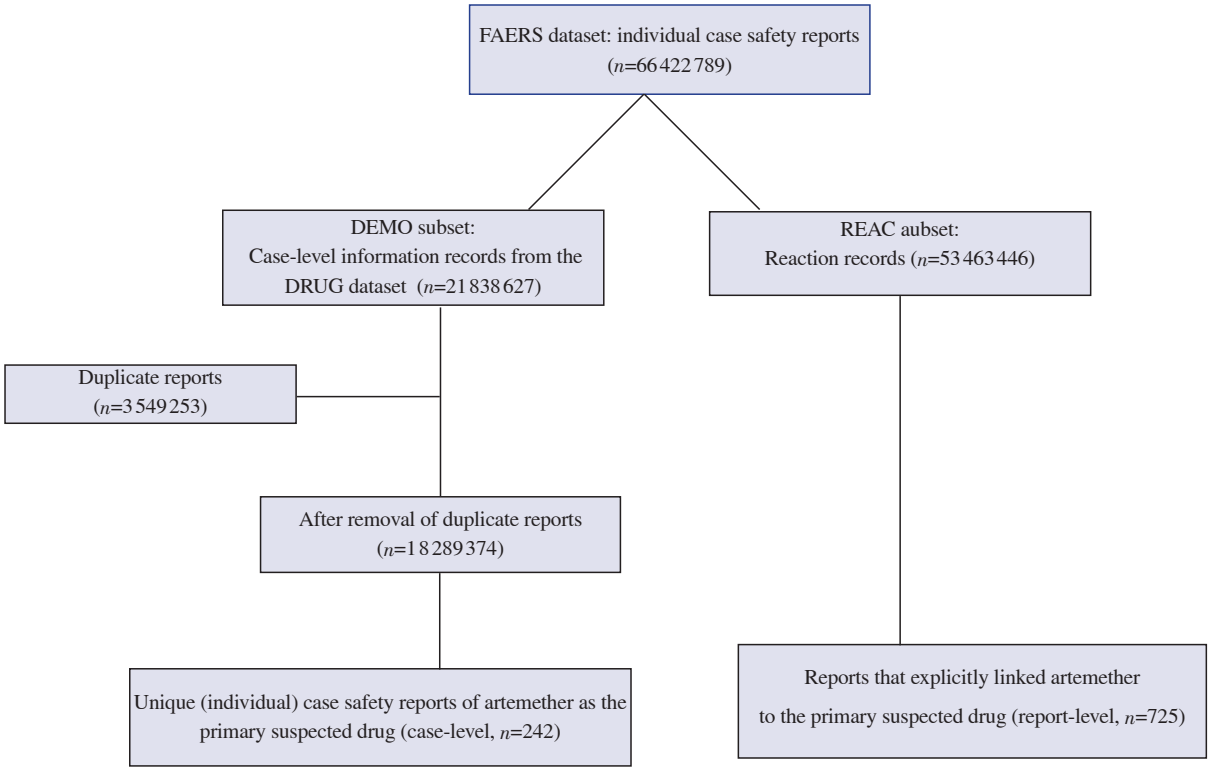

Figure 1. Flowchart of the study. FAERS: FDA adverse event reporting system.

were standardized to enhance transparency, reproducibility, and interpretability of the analysis and findings.

2.4. Flowchart of data processing and AE analysis

A comprehensive data processing workflow was implemented to identify and analyze artemether-related AEs. As depicted in Figure 1, the initial FAERS dataset comprised 66 422 789 individual case safety reports (ICSRs). A subset, DEMO, which are case-level information records (*n*=21 838 627), focused on artemether-related records, from which 3 549 253 duplication records were removed, yielding 18 289 374 unique reports for safety analysis.

Among these, 242 reports identified artemether as the primary suspected drug (PS) within the DRUG dataset. In parallel, 53 463 446 reaction records (REAC dataset) were reviewed, yielding 725 reports that explicitly linked artemether to suspected AEs.

Subsequently, the refined dataset was segmented into three core analytical domains: 1. Clinical characteristics–demographic and drug-specific profiles; 2. Signal detection–evaluation of disproportionality metrics; 3. Stratification and time-to-onset analysis – identification of variations based on demographic subgroups and temporal AE patterns (Temporal AE patterns refer to time-related trends in adverse event occurrence, reflecting the distribution of time intervals between the administration of artemether and the onset of reported adverse events).

This analytical framework facilitated a detailed exploration of the safety profile of artemether in a real-world pharmacovigilance context.

3. Results

3.1. Characteristics of reported artemether related AEs

Table 2 presents a summary of demographic and clinical characteristics from 242 AE reports associated with artemether. Among these, 47.1% (*n*=114) were male, 45.0% (*n*=109) were female, while sex was not defined for 7.9% (*n*=19) cases.

Age distribution showed that the majority of reports originated from individuals aged 18-65 years (134/242, 55.4%), followed by those under 18 years (47/242, 19.4%), and patients aged ≥65 years (8/242, 3.3%); age was not specified for 53 cases (21.9%).

In terms of clinical severity, 39.7% (96/242) of the reported events led to hospitalization, 9.5% (23/242) were life-threatening, 5.4% (13/242) resulted in death, and 42.1% (102/242) were categrized as other serious outcomes such as severe allergic reactions, organ dysfunctions, or laboratory abnormalities requiring urgent intervention but not resulting in hospitalization or death according to the FDA definitions.

Geographic distribution showed that France accounted for the highest number of reports (23.1%, 56/242), followed by Japan and the United States (each 7.9%, 19/242), Ghana (5.8%, 14/242), and Germany (5.0%, 12/242), while the remaining 101 cases were reported from other countries.

As for occupation, physicians and other healthcare professionals each contributed to 32.6% (79/242) of the reports. Reports from pharmacists and consumers constituted 15.7% (38/242) and 8.7% (21/242), respectively.

The reporting time ranged from 2010 to 2024. The years 2020, 2021, and 2022 each contributed between 19 and 23 reports, while 2024 had only 6 reports.

Table 2. Characteristics of adverse events reported for artemether (n=242).

Number of events	n (%)
Sex	
Male	114 (47.1)
Female	109 (45.0)
Unknown	19 (7.9)
Age, years	
<18	47 (19.4)
≥18 and<65	134 (55.4)
≥65	8 (3.3)
Unknown	53 (21.9)
Serious outcome	
Death	13 (5.4)
Hospitalization	96 (39.7)
Life-threatening condition	23 (9.5)
Disability	8 (3.3)
Others	102 (42.1)
Reportting countries	
France	56 (23.1)
Japan	19 (7.9)
United States	19 (7.9)
Ghana	14 (5.8)
Germany	12 (5.0)
Other countries/regions	122 (50.3)
Reporter	
Physician	79 (32.6)
Consumer	21 (8.7)
Health professional	38 (15.7)
Pharmacists	19 (7.9)
Other health-professional	79 (32.6)
Unknown	6 (2.5)

3.2. PT by SOC for artemether AE signals

Table 3 presents the PTs associated with artemether-related AEs, categorized by SOC, along with corresponding signal detection metrics including ROR with 95% Confidence intervals (*CI*), Information Component (IC), Proportional Reporting Ratio (PRR), and EBGM.

The strongest signal was observed for haemolytic anaemia under the SOC of "blood and lymphatic system disorders", with an ROR of 398.72 (95% *CI* 290.72-546.84), a high IC of 8.55, and an EBGM of 374.32 indicating a robust statistical association between artemether use and the occurrence of haemolytic anaemia. Other notable signals in this SOC included haemolysis (ROR: 152.67; 95% *CI* 89.91-259.24) and intravascular haemolysis (ROR: 436.02; 95% *CI* 139.83-1359.64), both demonstrating strong signal intensity across all statistical metrics.

In the SOC of "gastrointestinal disorders", vomiting exhibited a moderate signal, with an ROR of 3.18 (95% *CI* 1.12-8.01). Additional hematologic PTs, such as anaemia and thrombocytopenia, showed comparatively lower RORs (both 3.00), but still reflected potential associations warranting further investigation. Lower RORs with 3.00 (95% *CI* 1.43-6.33) and 3.00 (95% *CI* 1.12-8.01), but still reflected potential associations warranting further investigation.

These findings underscore the variation in signal intensity among different adverse events associated with artemether, highlighting blood-related toxicities as the predominant concern across multiple signal detection methodologies.

The IC and EBGM are Bayesian disproportionality measures used to identify potential drug–event associations. A signal is considered positive when the lower limit of the 95% *CI* exceeds the predefined threshold (IC025>0 or EBGM05>2), indicating a higher-than-expected reporting frequency.

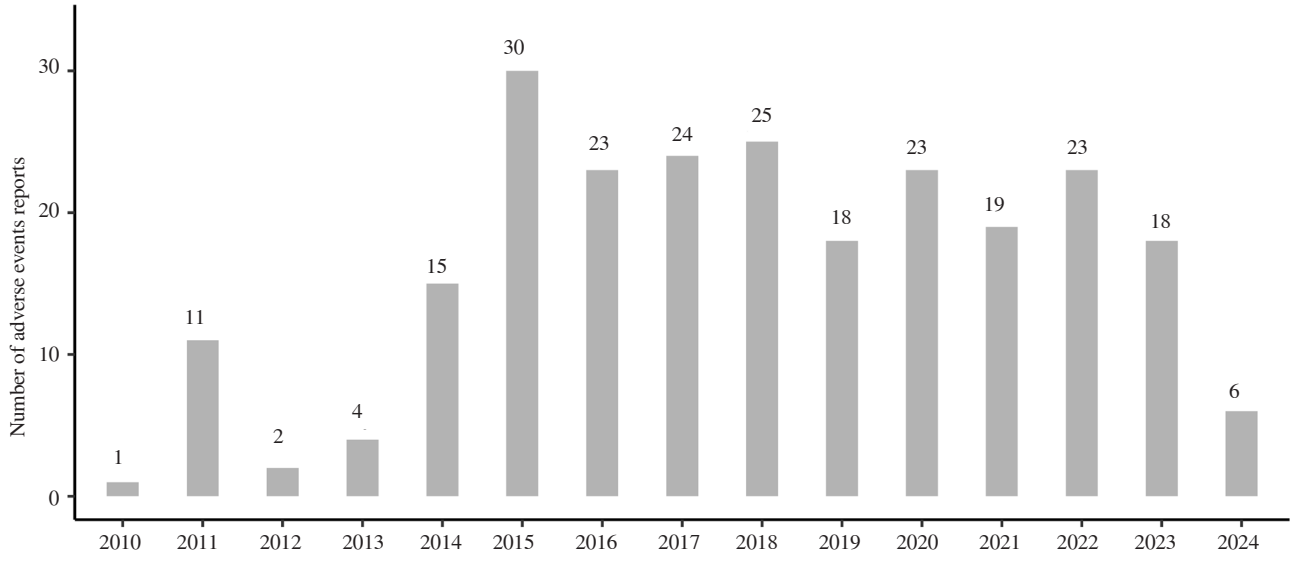

Figure 2. Trends in artemether-related adverse envent reports from 2010 to 2024.

Table 3. Preferred terms associated with artemether-related adverse events.

SOC terms	Preferred terms	*N*	ROR (95% *CI*)	IC (IC025)	PRR (χ^2)	EBGM (EBGM05)
Blood and lymphatic system disorders	Haemolytic anaemia	41	398.72 (290.72-546.84)	8.55 (8.09)	376.23 (15 267.54)	374.32 (287.37)
	Haemolysis	14	152.6 (89.91-259.24)	7.22 (6.47)	149.74 (2 064.5)	149.44 (95.95)
	Anaemia	7	3 (1.43-6.33)	1.58 (0.55)	2.99 (9.27)	2.99 (1.6)
	Thrombocytopenia	4	3 (1.12-8.01)	1.58 (0.28)	2.99 (5.29)	2.99 (1.31)
	Intravascular haemolysis	3	436.02 (139.83-1359.64)	8.75 (7.3)	434.22 (1 289.05)	431.67 (166.68)
Cardiac disorders	Bradycardia	3	4.56 (1.47-14.18)	2.18 (0.74)	4.55 (8.31)	4.55 (1.76)
Eye disorders	Ocular hyperaemia	3	5.69 (1.83-17.68)	2.5 (1.06)	5.67 (11.54)	5.67 (2.19)
Gastrointestinal disorders	Vomiting	16	2.9 (1.77-4.76)	1.52 (0.81)	2.86 (19.52)	2.86 (1.89)
General disorders and administration site conditions	Pyrexia	27	6.6 (4.49-9.69)	2.68 (2.12)	6.39 (123.47)	6.39 (4.63)
	Asthenia	18	4.02 (2.52-6.42)	1.98 (1.31)	3.95 (39.86)	3.95 (2.67)
	Chills	9	6.33 (3.28-12.22)	2.65 (1.73)	6.27 (39.93)	6.27 (3.62)
	Swelling face	6	7.71 (3.45 17.23)	2.94 (1.84)	7.66 (34.77)	7.66 (3.91)
	Drug resistance	4	13.26 (4.96-35.42)	3.72 (2.43)	13.19 (45.07)	13.19 (5.79)
Hepatobiliary disorders	Jaundice	7	20.97 (9.96-44.16)	4.38 (3.35)	20.78 (131.83)	20.78 (11.14)
	Hepatocellular injury	5	27.86 (11.56-67.16)	4.79 (3.61)	27.68 (128.56)	27.67 (13.25)
	Hepatitis	3	9.81 (3.16-30.5)	3.29 (1.84)	9.78 (23.64)	9.78 (3.78)
	Cholestasis	3	13.23 (4.26-41.13)	3.72 (2.27)	13.18 (33.78)	13.18 (5.1)
	Liver injury	3	11.9 (3.83-36.98)	3.57 (2.12)	11.85 (29.82)	11.85 (4.59)
Infections and infestations	*Plasmodium falciparum* Infection	11	8 279.27 (4421.69-15502.3)	12.84 (11.96)	8 153.67 (80 701.67)	7 338.4 (4341.82)
	Malaria	11	1 245.65 (683.37-2 270.59)	10.24 (9.39)	1 226.77 (13 251.1)	1 206.61 (730.12)
	Malaria relapse	6	110 993.06 (31 255.12-394 158.08)	15.43 (14.03)	110 074.5 (264 174.05)	44 030.4 (15 248.78)
Injury, poisoning and procedural complications	Product use in unapproved indication	9	3.44 (1.78-6.64)	1.77 (0.85)	3.41 (15.39)	3.41 (1.97)
	Foetal exposure during pregnancy	7	7.2 (3.42-15.16)	2.84 (1.81)	7.14 (37.03)	7.14 (3.83)
Investigations	Blood lactate dehydrogenase increased	5	24.61 (10.21-59.31)	4.61 (3.43)	24.44 (112.41)	24.44 (11.7)
	Haemoglobin decreased	5	3.95 (1.64-9.52)	1.97 (0.79)	3.93 (10.93)	3.93 (1.88)
	Blood bilirubin increased	4	11.95 (4.47-31.92)	3.57 (2.28)	11.88 (39.89)	11.88 (5.22)
	Electrocardiogram qt prolonged	3	6.99 (2.25-21.74)	2.8 (1.35)	6.97 (15.34)	6.97 (2.70)
Metabolism and nutrition disorders	Decreased appetite	9	3.31 (1.71-6.38)	1.71 (0.79)	3.28 (14.31)	3.28 (1.89)
Nervous system disorders	Headache	14	1.86 (1.09-3.15)	0.88 (0.13)	1.84 (5.43)	1.84 (1.18)
	Seizure	5	3.79 (1.57-9.13)	1.91 (0.73)	3.77 (10.19)	3.77 (1.81)
	Coma	3	5.17 (1.66-16.08)	2.37 (0.92)	5.16 (10.06)	5.16 (2.00)
	Nervous system disorder	3	7.67 (2.47-23.84)	2.93 (1.49)	7.64 (17.33)	7.64 (2.96)
Pregnancy, puerperium and perinatal conditions	Premature baby	8	21.38 (10.65-42.91)	4.4 (3.43)	21.15 (153.63)	21.15 (11.8)
	Spontaneous abortion	5	10.15 (4.21-24.45)	3.33 (2.15)	10.08 (40.94)	10.08 (4.83)
	Premature labour	4	54.31 (20.32-145.16)	5.75 (4.46)	54.02 (208.01)	53.98 (23.71)
Renal and urinary disorders	Chromaturia	4	14.5 (5.43-38.75)	3.85 (2.56)	14.43 (50.00)	14.43 (6.34)
	Haematuria	3	7.05 (2.27-21.9)	2.81 (1.36)	7.02 (15.5)	7.02 (2.72)
Skin and subcutaneous tissue disorders	Pruritus	9	2.14 (1.11-4.13)	1.09 (0.17)	2.12 (5.39)	2.12 (1.23)
	Skin discolouration	3	5.39 (1.73-16.75)	2.43 (0.98)	5.37 (10.68)	5.37 (2.08)
	Stevens-Johnson Syndrome	3	10.94 (3.52-34.02)	3.45 (2.00)	10.9 (26.99)	10.9 (4.22)
	Rash pruritic	3	4.78 (1.54-14.85)	2.25 (0.80)	4.76 (8.92)	4.76 (1.84)

N represents the number of adverse event reports at the preferred term level, rather than the number of unique cases. One individual report may involved with several preferred terms, the cumulative *N* across preferred terms is 313, which exceeds the number of unique cases (n=242). ROR: Reporting Odds Ratio, *CI*: Confidence interval.

3.3. Temporal trends in artemether related AE reports

Figure 2 illustrates the temporal distribution of artemether-related AE reports from 2010 to 2024. A notable upward trend was observed beginning in 2014, culminating in a peak in 2015 with 30 reported cases. It then remained relatively stable from 2016 to 2023, with the number of annual reported cases fluctuating between 18 and 25.

A decline was noted in 2024, with only 6 reports submitted. This number marks the lowest in the past decade. Such a trend may be attributed to reduced drug utilization, changes in reporting behavior, or improved safety measures.

These findings, taken together, raise important considerations for

SOC terms	*N*	ROR (95% *CI*)
Pregnancy, puerperium and perinatal conditions	28	9.22 (6.32-13.45)
Blood and lymphatic system disorders	87	7.80 (6.24-9.76)
Hepatobiliary disorders	30	4.64 (3.22-6.69)
Congenital, familial and genetic disorders	6	2.70 (1.21-6.04)
Renal and urinary disorders	16	1.19 (0.73-1.96)
Infections and infestations	44	1.15 (0.85-1.56)
Investigations	49	1.09 (0.81-1.45)
General disorders and administration site conditions	131	1.04 (0.86-1.25)
Nervous system disorders	63	1.02 (0.79-1.32)
Skin and subcutaneous tissue disorders	40	1.02 (0.74-1.40)
Metabolism and nutrition disorders	15	0.95 (0.57-1.59)
Ear and labyrinth disorders	3	0.95 (0.31-2.96)
Eye disorders	13	0.88 (0.51-1.53)
Gastrointestinal disorders	54	0.85 (0.65-1.13)
Injury, poisoning and procedural complications	55	0.79 (0.60-1.04)
Respiratory, thoracic and mediastinal disorders	25	0.71 (0.47-1.05)
Vascular disorders	11	0.69 (0.38-1.26)
Cardiac disorders	12	0.61 (0.35-1.08)
Immune system disorders	5	0.61 (0.25-1.48)
Reproductive system and breast disorders	3	0.50 (0.16-1.54)
Product issues	5	0.43 (0.18-1.04)
Musculoskeletal and connective tissue disorders	15	0.38 (0.23-0.63)
Psychiatric disorders	13	0.30 (0.17-0.52)
Surgical and medical procedures	1	0.10 (0.01-0.71)
Neoplasms benign, malignant and unspecified (include cysts and polyps)	1	0.05 (0.01-0.36)

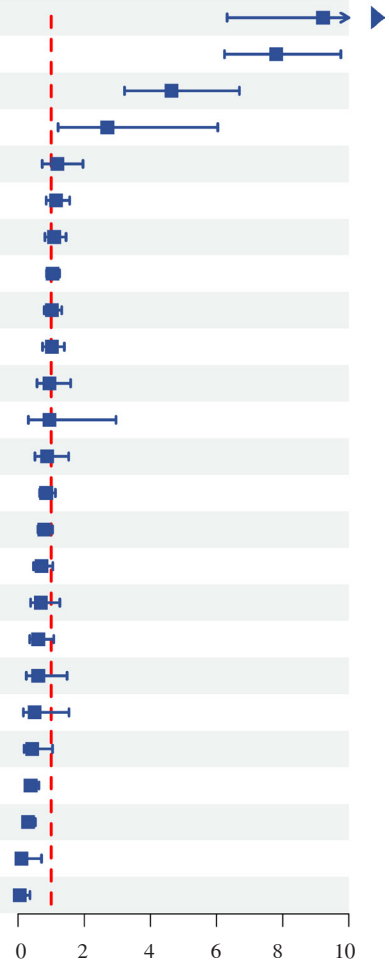

Figure 3. Risk of adverse events by system organ class (SOC) for artemether. *N* represents the number of adverse events at the SOC level, rather than unique case numbers. A single adverse event may be classified into several SOCs (*N*=725). ROR: Reporting odds ratio, *CI*: Confidence interval.

clinical safety. They point to the necessity of sustained monitoring and prompt reporting of artemether-related AEs. Such efforts are essential to ensure ongoing pharmacovigilance and informed risk evaluation in real-world settings.

3.4. Risk of AEs by SOC for artemether

Figure 3 displays the RORs and corresponding 95% *CI*s for various SOCs associated with artemether-related AEs. The highest risk signal occurred in the pregnancy-related SOC (ROR 9.22, 95% *CI* 6.32-13.45). This suggests a markedly increased risk of adverse outcomes in that category. Blood and lymphatic system disorders also showed a strong signal (ROR 7.80, 95% *CI* 6.24-9.76). These findings reinforce hematological toxicity as a key safety concern.

Hepatobiliary disorders showed a notable signal (ROR 4.64, 95% *CI* 3.22-6.69), indicating possible hepatic involvement. This association was weaker than those observed in pregnancy- and blood-related categories. In contrast, general disorders (ROR 1.04, 95% *CI* 0.86-1.25) and nervous system disorders (ROR 1.02, 95% *CI* 0.79-1.32) showed no significant risk elevation. The lowest RORs were observed in reproductive (ROR 0.50, 95% *CI* 0.16-1.54), psychiatric (ROR 0.30, 95% *CI* 0.17-0.52), and neoplasm-related disorders (ROR 0.05, 95% *CI* 0.01-0.36), suggesting minimal or no association with artemether.

These findings underscore the heterogeneity of risk across SOCs and emphasize the need for heightened clinical awareness in specific domains, particularly in reproductive, hematologic, and hepatic systems.

3.5. ROR for PT by SOC for artemether

Figure 4 displays the RORs and corresponding 95% *CI*s for specific PTs of AEs associated with artemether, stratified by SOC.

The most elevated ROR was observed for reticulocytopenia under the "blood and lymphatic system disorders" SOC, with a ROR value of 1 337.92 (95% *CI* 39.81-5 427.56), indicating a very strong

Preferred terms	*N*	ROR (95% *CI*)
Reticulocytopenia	2	1337.92 (328.81–5427.56)
Coombs negative haemolytic anaemia	3	1222.77 (111.88–4057.62)
Jaundice acholuric	1	915.58 (47.00–1612.10)
Intravascular haemolysis	3	436.02 (33.18–1359.64)
Haemolytic anaemia	4	398.72 (29.78–1345.69)
Coombs positive haemolytic anaemia	2	374.57 (86.90–1047.79)
Haemolysis	14	152.67 (19.87–250.26)
Autoimmune haemolytic anaemia	2	52.63 (1.18–212.51)
Glucose-6-phosphate dehydrogenase deficiency	2	736.18 (82.42–2688.42)
Congenital umbilical hernia	1	234.03 (32.02–1692.29)
Cleft lip	1	43.53 (2.36–323.76)
Polydactyly	1	87.65 (5.82–569.13)
Cleft palate	1	41.85 (3.96–238.16)
Conjunctival pallor	1	53.40 (2.42–324.16)
Gingival erosion	1	304.91 (27.96–2174.83)
Gastrointestinal hypermotility	1	198.07 (29.79–1111.37)
Reflux gastritis	1	72.47 (10.78–515.67)
Noninfective gingivitis	1	62.43 (7.17–444.82)
Vanishing bile duct syndrome	1	58.65 (8.02–419.05)
Malaria relapse	6	110993.03 (361275.12–394158.08)
Malaria recrudescence	3	36779.63 (2736.58–11291.42)
Plasmodium falciparum infection	11	8279.27 (714.00–15502.28)
Cerebral malaria	8	6367.65 (517.02–12850.21)
Plasmodium vivax infection	2	8367.51 (380.98–27229.73)
Infection protozoal	11	1749.63 (540.43–12767.56)
Malaria	11	225.54 (34.89–2270.59)
Mumps	1	24.49 (5.33–147.77)
Malaria antibody test positive	1	1446.95 (347.18–12555.27)
Parasitic test positive	1	6689.38 (913.54–51812.21)
Parasite blood test positive	1	2449.48 (343.06–18022.82)
Salmonella test positive	1	1148.19 (157.90–8287.86)
Liver palpable	1	113.41 (14.53–802.53)
Blood smear test abnormal	1	709.74 (145.63–7567.56)
Metabolic function test abnormal	1	205.12 (31.40–2620.26)
Coombs test positive	1	291.64 (40.08–2051.60)
Haemoglobin decreased	1	108.19 (9.74–755.57)
Limb deformity	1	49.68 (9.95–253.43)
Dysmetria	1	142.95 (20.07–1016.28)
Placenta praevia haemorrhage	1	740.23 (103.58–5171.08)
Maternal condition affecting foetus	1	320.44 (7.84–2249.47)
Uterine contractions abnormal	2	292.76 (21.04–2899.88)
Abortion	2	54.61 (3.96–129.16)
Premature labour	4	63.22 (3.39–214.56)
Product counterfeit	1	55.37 (6.32–96.04)
Costovertebral angle tenderness	1	47.77 (6.16–341.78)
Nasopharyngitis	1	48.88 (4.89–467.02)
Nasal flaring	1	689.95 (97.53–5021.71)
Purpura fulminans	1	334.20 (46.72–2388.58)
Photodermatosis	1	185.12 (5.97–1319.19)
Extremity necrosis	1	47.19 (6.35–335.72)

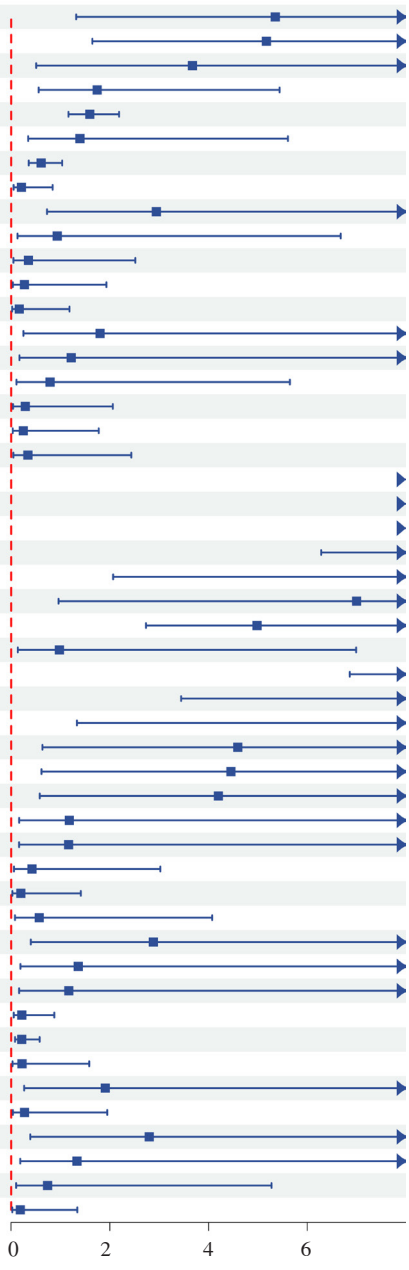

Figure 4. ROR for advese events associated with artemether by preferred terms. *N* represents preferred term-level adverse events, and this figure only shows a subset of preferred terms that met the predefined signal detection criteria (the cumulative *N*=124). ROR: Reporting odds ratio, *CI*: Confidence interval.

association with artemether exposure. Similarly, coombs positive haemolytic anaemia exhibited a markedly high ROR of 1322.77 (95% *CI* 711.88-4057.64), and jaundice acholic also showed a significant signal (ROR: 9.18; 95% *CI* 1.56-60.12).

In the SOC of "congenital, familial, and genetic disorders", glucose-6-phosphate dehydrogenase deficiency demonstrated a strong signal with an ROR of 735.86 (95% *CI* 368.42-1428.42), underscoring the relevance of genetic predisposition in artemether-related AEs.

Under the SOC of "Infections and Infestations", extremely high RORs were observed for malaria recurrence (ROR: 36797.60; 95% *CI* 27.37-101946) and *P. falciparum* infection (ROR: 8279.27; 95% *CI* 146.00-15502.28). Similarly, cerebral malaria and *P. vivax* infection also displayed robust associations with RORs of 6689.63 (95% *CI* 161.75-25801.28) and 3467.61 (95% *CI* 160.68-22879.73), respectively.

These results highlight a cluster of PTs—particularly within hematologic and infectious categories—that are strongly associated with artemether usage. Such findings underscore the importance of vigilant monitoring, especially in patients with predisposing conditions like glucose-6-phosphate dehydrogenase deficiency or existing parasitic infections.

Subgroup	Preferred terms	*N*	ROR (95% *CI*)
Male	Haemolytic anaemia	22	381.36 (247.06-588.66)
	Pyrexia	11	5.19 (2.84-9.47)
	Malaria	8	1 613.14 (790.27-3 285.34)
	Asthenia	8	3.74 (1.85-7.52)
	Haemolysis	7	136.68 (54.87-269.29)
	Plasmodium falciparum infection	6	7 912.68 (3 341.24-18 721.34)
	Dyspnoea	5	1.63 (0.67-3.94)
	Vomiting	5	2.42 (1.05-5.59)
	Headache	5	2.04 (0.89-4.83)
	Hepatocellular Injury	4	41.42 (15.44-111.07)
	Blood lactate dehydrogenase increase	4	3.22 (1.23-8.78)
	Fatigue	4	1.03 (0.36-2.95)
	Haemoglobin decrease	4	5.79 (2.16-15.51)
	Chills	4	6.03 (2.25-16.17)
	Pruritus	4	2.33 (1.09-5.78)
	Decreased appetite	4	2.31 (1.02-5.24)
	Nausea	4	4.27 (1.67-3.41)
	Anaemia	4	3.45 (1.29-9.24)
	Blood bilirubin increased	3	14.29 (4.55-44.50)
	Condition aggravated	3	2.03 (0.65-6.43)
	Thrombocytopenia	3	3.99 (1.82-12.43)
	Drug resistance	3	18.79 (6.53-53.50)
	Rash	3	1.4 (0.45-4.37)
	Malaise	3	1.48 (0.47-4.61)
	Pain	3	1.02 (0.33-3.16)
Female	Haemolytic anaemia	19	435.11 (263.43-723.12)
	Pyrexia	16	8.36 (5.17-13.4)
	Vomiting	11	3.47 (1.86-6.18)
	Asthenia	10	4.42 (2.36-8.28)
	Headache	9	2.01 (1.04-3.72)
	Haemolysis	7	23.01 (10.72-45.149)
	Dyspnoea	6	1.7 (0.70-3.82)
	Plasmodium falciparum infection	5	8 735.24 (3 157.33-22 070.31)
	Chills	5	6.29 (2.35-16.65)
	Abortion spontaneous	5	12.25 (5.07-26.91)
	Decreased appetite	5	3.82 (1.58-9.23)
	Pain	5	1.17 (0.62-2.33)
	Pruritus	5	2.16 (0.89-5.21)
	Loss of consciousness	4	5.28 (1.57-14.14)
	Jaundice	4	30.13 (11.24-80.73)
	Nausea	4	6.71 (2.06-19.8)
	Premature labour	4	6.84 (2.54-18.13)
	Anaemia	3	2.83 (0.93-8.81)
	Peripheral swelling	3	2.9 (0.90-9.04)
	Foetal exposure during pregnancy	3	12.65 (4.06-39.42)
	Malaise	3	0.57 (0.27-1.35)
	Swelling face	3	6.29 (2.05-19.92)
	Hepatitis	3	21.61 (2.63-66.08)
	Acute kidney injury	3	4.94 (1.59-15.4)
	Dizziness	3	0.9 0 (0.29-2.81)

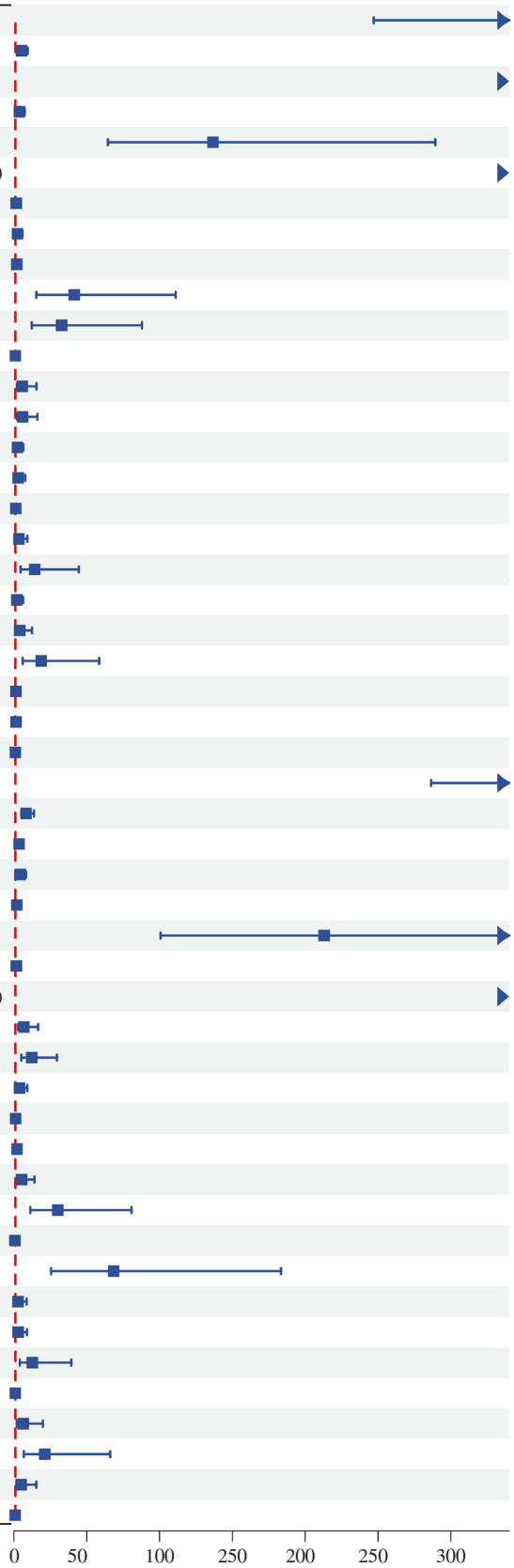

Figure 5. ROR for adverse event reports associated with artemether in male and female. The cumulative number 282 corresponds to preferred term-level adverse events stratified by sex. 114 reports were from male and 109 from female. Reports with missing or unknown sex information were excluded from this analysis. ROR: Reporting odds ratio, *CI*: Confidence interval for advese events associated with artemether by preferred terms.

3.6. Sex differences in AE signals associated with artemether

Figure 5 illustrates the RORs and 95% *CI*s for AE signals associated with artemether, stratified by sex. In male patients, haemolytic anaemia exhibited the strongest association, with an ROR of 381.36 (95% *CI* 247.06–588.66). Other prominent AEs in this group included pyrexia (ROR: 5.19; 95% *CI* 2.84–9.47) and malaria (ROR: 1613.14; 95% *CI* 792.07–3 285.34), indicating significant hematological and infectious event risks.

Among female patients, haemolytic anaemia also showed a high ROR of 455.11 (95% *CI* 286.43-723.12), consistent with the male subgroup. Notably, pyrexia (ROR: 8.36; 95% *CI* 5.07-13.80) and vomiting (ROR: 3.57; 95% *CI* 1.96-6.50) were also frequently reported. Furthermore, distinct female-specific AEs were observed: spontaneous abortion (ROR: 12.25; 95% *CI* 5.07-29.61) and premature labour (ROR: 68.44; 95% *CI* 25.54-183.41), both demonstrating substantial associations with artemether exposure.

Importantly, *P. falciparum* infection was markedly more frequent in females, with an ROR of 8 735.24 (95% *CI* 3 457.33-22 070.31), significantly higher than in males, suggesting a potential sex-based biological or clinical reporting difference.

These findings suggest that while certain AEs are common across sex—particularly hematological reactions—female patients may experience a higher frequency of specific events, particularly those related to reproductive and infectious conditions. These observations underscore the necessity for gender-sensitive risk assessment and monitoring in artemether pharmacovigilance.

3.7. Time distribution of AE reports for artemether

As for presents the distribution of artemether-related AE reports in the FAERS database based on time-to-onset (TTO), the analysis utilized predefined intervals (0–30, 31–60, 61–90, 91–120, 121–150, 151–180, 181–210, 211–240, 241–270, 271–300, 301–330, 331–360, and >360 days) to evaluate the temporal patterns of AE occurrence following drug administration.

Notably, positive case counts were observed in only three intervals: 0–30 days, 31–60 days, and >360 days. All other intervals reported zero cases and were omitted from the analysis to enhance clarity and focus.

The majority of AEs (94.37%, 67/71) occurred within the first 30 days post-treatment, indicating that artemether related AEs predominantly occurre early. A much smaller proportion of reports were recorded in the 31–60 day interval (2.82%, 2/71) and in the >360 day category (2.82%, 2/71), reflecting a sharp decline in reported AEs beyond the initial treatment period.

These results underscore the acute nature of most artemether-associated AEs and emphasize the importance of close monitoring during the first month of therapy.

4. Discussion

Based on AE reports submitted to the US Food and Drug Administration's FAERS database between 2010 and 2024, this study evaluated temporal trends, risk correlations, and reporting behaviors associated with artemether use. AEs were grouped using the MedDRA classification system, including SOC and PT, and signal detection was performed using RORs and standard pharmacovigilance metrics. Results indicated a marked rise in artemether-related AE reports beginning in 2014, with the highest number observed in 2015. The most prevalent events involved hematologic toxicity—primarily haemolytic anaemia and haemolysis—alongside hepatobiliary injury and adverse effects targeting the reproductive system. Notably, a greate proportion of pregnancy-related AEs, including premature labor and spontaneous abortion were reported, suggesting a possible sex-dependent susceptibility. Temporal analysis further revealed that the majority of AEs occurred within the first 30 days following initiation artemether treatment, emphasizing the need for enhanced clinical vigilance during early treatment windows.

Hepatic injury associated with artemether is hypothesized to result from oxidative stress, which disrupts hepatocellular homeostasis and initiates cell damage pathways[4]. Artemether metabolism in the liver can generate reactive oxygen species (ROS), contributing to antioxidant depletion, inflammation, and hepatocyte injury[5]. Additionally, mitochondrial involvement has been proposed, as ROS accumulation and impaired respiration may compromise mitochondrial function[6]. Mechanistically, artemether appears to interfere with mitochondrial electron transport, impairing ATP generation and exacerbating intracellular ROS load[7,8]. These synergistic insults to hepatocytes may culminate in a spectrum of hepatic outcomes, ranging from reversible metabolic alterations to severe, potentially fatal dysfunction][9].

Neurotoxicity related to artemether may stem from its ability to get through the blood-brain barrier and disrupt central nervous system (CNS) function[10]. This disruption is believed to involve heightened oxidative stress within neurons, compromising redox balance and neuronal viability[11]. Artemether exposure may alter neurotransmitter activity by interfering with dopaminergic, serotonergic, and GABAergic pathways essential for CNS regulation[12]. Such alterations could give rise to neurotoxic phenotypes, including cognitive or sensory changes. Additionally, disturbances in calcium homeostasis may promote neuronal hyperexcitability, contributing to symptoms such as dizziness or seizure activity[13].

Artemether-related hematologic AEs are thought to arise from two principal mechanisms: suppression of hematopoietic function and oxidative injury to erythrocytes[14]. Oxidative stress induced by artemether metabolites may lead to red blood cell membrane

destabilization and subsequent hemolysis[15]. Furthermore, interference with erythropoiesis may exacerbate anemia and other cytopenias[16]. These pathological changes impair oxygen delivery and hemostatic balance. Clinically, manifestations of hematologic toxicity may include fatigue, dyspnea, and heightened bleeding risk, particularly in patients undergoing procedures or with coagulation disorders[17].

Fetal toxicity may be attributed to transplacental passage of artemether and fetal exposure to active metabolites[18]. These metabolites may interfere with normal fetal development through oxidative stress and disruption of cellular processes. Artemether may also alter endocrine signaling during pregnancy, thereby contributing to developmental anomalies[19]. High metabolic demand organs in the fetus, such as the liver, kidneys, and CNS, may be particularly vulnerable to artemether-induced oxidative injury[20]. These mechanistic pathways may help to explain the observed pregnancy-related complications associated with artemether. Disruption of placental function by oxidative metabolites may impair fetal oxygen and nutrient supply, contributing to intrauterine growth restriction[21]. Concurrent modulation of maternal immune responses may also elevate pregnancy risk. The spectrum of artemether-related pregnancy outcomes includes spontaneous abortion, preterm labor, and fetal malformations[22].

Artemether is metabolized primarily in the liver *via* cytochrome P450 enzymes, especially CYP3A4[23]. This enzyme plays a central role in the conversion of artemether to both active and potentially toxic metabolites[24]. These metabolites are responsible for both the therapeutic and adverse pharmacological effects of the drug[25]. Available data suggest that some metabolites may exhibit greater toxicity than artemether itself[26]. The formation of ROS during metabolism may contribute to cumulative organ injury, particularly in the liver and kidneys[27]. These findings support routine liver function testing and metabolic monitoring during treatment, especially in patients with pre-existing hepatic conditions or impaired cytochrome P450 function.

Immune-mediated reactions may contribute to artemether's toxicity profile. The drug may induce an inflammatory cytokine response, including events analogous to cytokine release syndrome observed with other drugs[28]. Elevated levels of IL-6, TNF-α, and IFN-γ may be implicated in systemic inflammation, capillary leak, and tissue injury[29]. These mechanisms may explain common nonspecific AEs such as rash and fever, as well as rare but severe reactions including anaphylaxis. Genetic predisposition or prior immune priming may influence individual susceptibility to such immune-mediated AEs[30].

Animal and *in vitro* studies support a dose-dependent relationship between artemether and organ-specific toxicities[31]. Preclinical data demonstrate that high-dose artemether induces hepatic and renal injury, consistent with clinical observations[32]. *In vitro* studies suggest that artemether may trigger immune responses through interactions with red blood cells, possibly explaining hematologic AEs[33]. Pharmacokinetic studies are needed to clarify variability in artemether metabolism and toxicity. Drug clearance may be modulated by patient-specific factors such as age, hepatic function, and concurrent medications[34]. Integrating pharmacokinetic data into clinical practice may support risk stratification and guide personalised dosing and monitoring strategies[35].

This study has several limitations. First, as FAERS is a spontaneous reporting system, underreporting, reporting bias, and variable report quality may influence the accuracy of the detected safety signals. Second, causality between artemether and the reported adverse events cannot be established because FAERS lacks detailed clinical information and denominator data on total drug exposure. Third, the data may be influenced by confounding factors such as concomitant medications, comorbidities, and demographic disparities that could not be fully adjusted for. Finally, time-to-onset analyses may be affected by incomplete or inconsistent date entries. Therefore, the findings should be interpreted with caution and validated through prospective clinical studies.

In conclusion, this pharmacovigilance analysis based on 15-year FAERS data identified important safety concerns associated with artemether use, particularly haematological toxicity—most notably haemolytic anaemia—hepatobiliary injury, and adverse pregnancy outcomes. The majority of AEs occurred within 30 days of treatment initiation, underscoring the need for early and vigilant clinical monitoring. Female patients exhibited a relative high susceptibility to reproductive complications, including spontaneous abortion. These findings highlight the need for sex-specific risk assessment, personalised treatment strategies, and further pharmacogenomic research to ensure the safer use of artemether, especially in malariaendemic settings.

Conflict of interest statement

The authors declare no conflicts of interest related to this work.

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Authors' contributions

BJ extracted FAERS data, conducted the primary statistical analyses, and contributed to the initial drafting of the manuscript. JXW participated in data collection, data cleaning, and visualization, and assisted in interpreting the pharmacovigilance findings. XCL contributed to literature review, methodological refinement, and verification of analytical procedures. LLH supported data validation, helped refine the study design, and provided critical revisions to improve the intellectual content of the manuscript. TTH assisted with figure preparation, data quality assessment, and technical support throughout the study. BN conceived and designed the overall study, supervised all stages of data analysis and interpretation, critically revised the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript.

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