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Research Article

Postmarketing Safety Concerns With Caplacizumab: A Real-World Pharmacovigilance Study Based on the FDA Adverse Event Reporting System Database

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Abstract

Objective: To analyze data from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) database to characterize the adverse effects of caplacizumab, including associated adverse events (AEs) and safety signals in real-world clinical practice. and obtain evidence to support the rational use of this drug in the treatment of thrombotic thrombocytopenic purpura (TTP). **Methods:** Postmarketing AE reports associated with caplacizumab were retrieved from the FAERS database. Safety signals were identified using four disproportionality analysis methods: the reporting odds ratio, proportional reporting ratio, Bayesian Confidence Propagation Neural Network (BCPNN), and multi-item gamma Poisson shrinker. The Weibull distribution was used to analyze the onset time of AEs, and subgroup analyses were performed according to sex, age group, and reporter type. **Results:** In total, 1144 reports involving caplacizumab were analyzed. Most AEs were nonserious. Among the 401 reports with documented onset times, 162 (40.4%) described AEs occurring within 7 days of administration. Common bleeding-related events (e.g., epistaxis, gingival bleeding, gastrointestinal hemorrhage, heavy menstrual bleeding, and vaginal hemorrhage) were consistent with product labeling. Decreases in platelet count and in disintegrin and metalloproteinase with thrombospondin type 1 motif 13 (ADAMTS13) activity were interpreted as manifestations of the underlying disease (acquired TTP) rather than drug-induced AEs. Newly identified safety signals included contusion, injection site pain, injection site bruising, injection site erythema, injection site haemorrhage, pruritus and rash. **Conclusions:** These findings underscore the importance of pharmacovigilance and postmarketing surveillance for caplacizumab. Clinicians should closely monitor bleeding events and injection site reactions during treatment. To ensure the safe use of caplacizumab, the mechanisms underlying these potential signals should be elucidated, and targeted monitoring strategies should be developed.

Keywords: caplacizumab; thrombotic thrombocytopenic purpura; pharmacovigilance; adverse drug reaction reporting system; data mining; product surveillance; postmarketing

1. Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare but severe thrombotic microangiopathy characterized by microangiopathic hemolytic anemia, thrombocytopenia, neuropsychiatric symptoms, fever, and renal impairment [1,2], with its pathogenesis mainly related to low A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, member 13 (ADAMTS13) activity [3]. TTP is classified as congenital or immune-mediated (acquired), with acquired TTP (aTTP) having a share of ~95% [4,5].

Caplacizumab is a humanized nanobody targeting von Willebrand factor (vWF)–platelet interactions and inhibiting platelet adhesion [6]. Phase II TITAN and Phase III HERCULES trials showed that caplacizumab + standard care shortened the platelet count response time by 39% ($p < 0.001$), reduced aTTP-related mortality/exacerbations, and decreased intensive care unit (ICU) and hospital stay length [3,7]. Caplacizumab was approved by the U.S. Food and Drug Administration (FDA) in February 2019 (CABLIVI®) for treating aTTP in adults in combination with plasma exchange and immunosuppression.

The International Society on Thrombosis and Haemostasis (ISTH) guidelines recommend adding corticosteroids, rituximab, and caplacizumab to therapeutic plasma exchange for acute aTTP [8]. Based on prescribing information, common adverse events (AEs; incidence >15%) include epistaxis, headache, and gingival bleeding. However, these AEs originate from clinical trials with strict criteria and may differ from real-world observations.

The FDA Adverse Event Reporting System (FAERS) is a public platform for postmarketing AE surveillance [9] used in numerous drug safety studies [10,11,12]. The Capla 1000+ study (n = 1015) reported a 21% incidence of caplacizumab-related AEs in real-world settings [13]. FAERS-based analysis offers complementary insights by capturing spontaneous reports from a broader unselected real–world population than randomized controlled trial (RCT) cohorts. Therefore, we herein analyzed reports

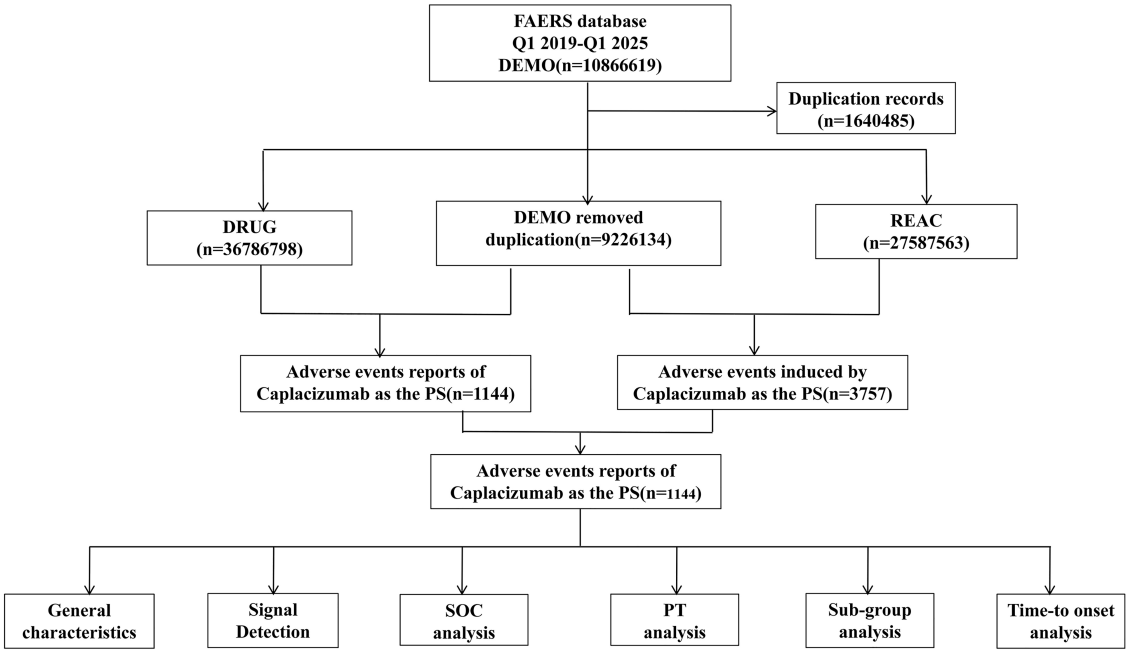


Fig. 1. Flowchart for identifying caplacizumab-associated adverse events (AEs) in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) database.

on the AEs of caplacizumab extracted from the FAERS database to provide a reference for the rational and safe clinical use of this drug.

2. Materials and Methods

2.1 Data Sourcing and Deduplication

Data from the first quarter of 2019 to the first quarter of 2025 (25 quarters in total) were extracted from the FAERS database, cleaned, and analyzed to obtain reports on the AEs of the listed drugs (10,866,619 copies). According to the two-step deduplication method recommended by the FDA, the case number (CASEID), date when the report was received by the FDA (FDA_DT), and unique primary identification code (PRIMARYID) fields from the population information table were selected. For reports with the same CASEID, the one with the largest FDA_DT value was retained. For cases with the same CASEID and FDA_DT, the report with the largest PRIMARYID value was retained. After deduplication, the records were filtered based on the CASEID in the deletion report list, which resulted in 1,640,485 reports. Then, caplacizumab was regarded as the primary suspected drug. Using "caplacizumab" and "CABLIVI" as search terms, we matched the product composition and drug name fields in the database for searching. Eventually, 1144 reports related to caplacizumab AEs were obtained. The retrieved AE signals were classified and analyzed using the system organ class (SOC) and preferred terms (PTs) in the 26.1 edition of the Medical Dictionary for Regulatory Activities (MedDRA). The flowchart for identifying caplacizumab-associated AEs in the FAERS database is illustrated in Fig. 1.

2.2 Data Analysis

Several pharmacovigilance methodologies, including the reporting odds ratio (ROR), proportional reporting ratio (PRR), multi-item gamma Poisson shrinker (MGPS), and Bayesian confidence propagation neural network (BCPNN), were employed to evaluate significant correlations between caplacizumab and AEs. AEs exceeding the positive threshold (as defined in the main text) in all of the four methods were identified as possible signals. In addition, Weibull distribution modeling was used to analyze the onset times of AEs. Data processing was carried out using SAS v.9.4 (SAS Institute Inc., Cary, North Carolina). The results were analyzed based on **Supplementary Tables 1 and 2**. Then, statistical analyses were conducted on the basic information, clinical characteristics, reporting sources, and occurrence times, frequencies, and intensities of AEs using Graphpad Prism v.9.1 (GraphPad Software, San Diego, CA, USA) and Excel (Microsoft Corporation, Redmond, WA, USA).

2.3 Classification of Reported Events

A critical methodological consideration in the pharmacovigilance studies of caplacizumab is the distinction between true adverse drug reactions and manifestations of the underlying disease (aTTP), which is characterized by microangiopathic hemolytic anemia, severe thrombocytopenia, and severely decreased ADAMTS13 activity [1,2]. Therefore, the following PTs were a priori classified as disease manifestations rather than drug-induced AEs: decreased platelet count, decreased ADAMTS13 activity, abnormal ADAMTS13 activity, TTP, decreased hemoglobin,

increased blood lactate dehydrogenase, and related laboratory abnormalities. These PTs were included in descriptive analysis (Tables 1 and 2) to provide a complete picture of reported events but were excluded from the final list of newly identified drug-related safety signals.

Conversely, PTs were mechanistically plausible as drug-related (e.g., bleeding events and injection site reactions) and those not explained by the natural history of TTP were retained for signal detection. Product use in an unapproved indication was classified as a prescribing pattern indicator rather than as an AE, as it reflects clinical practice patterns (e.g., empiric use before diagnostic confirmation) rather than drug toxicity.

3. Results

3.1 Baseline Information Extracted From AE Reports

After cleaning, 1144 AEs reports were retained, with their baseline characteristics listed in Table 1. Women accounted for a greater fraction of these reports (57.90%) than men (24.40%). According to age, individuals aged 18–65 had a greater share (60.2%) than those aged 65–85 (11.20%). The United States reported the highest number of AEs cases (85.10%), followed by Germany (3.3%) and France (2.9%) (Fig. 2A). In terms of AEs outcomes, prolonged hospital stay and death had shares of 15.10% and 4.8%, respectively, with most cases (79.00%) having other outcomes. Most reports were made by consumers themselves (50.70%) and physicians (30.90%). Serious and nonserious AEs had shares of 35.70% and 64.30%, respectively. Nonfatal and fatal AEs had shares of 95.20% and 4.8%, respectively. Since the approval of caplacizumab by the FDA in 2019, the number of AE reports initially increased, peaked in 2022 (217 cases), and decreased with the increasing popularity of this drug, with 63 cases reported in the first quarter of 2025 (Fig. 2B). Among the concomitant drugs (**Supplementary Table 3**), those with the highest occurrence frequency were rituximab (n = 41), prednisone (n = 32), and rituxan (n = 30).

3.2 Signal Detection Related to SOC Levels

Fig. 3 and Fig. 4 present the AEs of caplacizumab at the SOC level with a positive ROR signal in the FAERS database. The caplacizumab-associated AEs meeting the ROR criterion (lower limit of 95% confidence interval (CI >1, $n \geq 3$) were associated with seven SOCs, all of which showed significant differences. Among them, the top three SOCs in terms of occurrence frequency were investigations [n = 761, ROR (95% CI) = 4.16 (3.84–4.5)]; injury, poisoning, and procedural complications [n = 723, ROR (95% CI) = 1.68 (1.55–1.82)]; and respiratory, thoracic, and mediastinal disorder [n = 197, ROR (95% CI) = 1.16 (1.01–1.34)]. Among these seven types of systems, respiratory, thoracic, and mediastinal disorders, and reproductive system and breast disorders are consistent with those described in the manual. However, investigation, injury, poisoning, and procedural complications, blood and lymphatic system disorders, vascular disorders, and surgical and medical procedures are not mentioned in the manual.

3.3 Signal Detection Related to PT Levels

We identified caplacizumab-related AEs using four signal detection algorithms (ROR, PRR, BCPNN, and MGPS) and ranked signals by frequency (Table 2). The most common PT was product use in an unapproved indication (n = 373), which was analyzed separately as a prescribing pattern (Section 3.3.3). Frequent disease-related PTs included decreased platelet count (n = 103) and decreased ADAMTS13 activity (n = 98). Common drug-related AEs were epistaxis (n = 100), contusion (n = 68), injection site pain (n = 56) and injection site bruising (n = 50). Bleeding events matched the product label, whereas contusion and injection-site reactions (pain, bruising, erythema, rash, hemorrhage, and pruritus) represent new safety signals. Crucially, thrombocytopenia, reduced ADAMTS13 activity, and TTP are manifestations of the underlying aTTP, not drug-induced AEs. Details of PT-level signals are listed in **Supplementary Table 4**, and signal strengths are listed in **Supplementary Table 5**. Within reproductive system and breast disorders, the most frequent PTs were heavy menstrual bleeding (n = 16), vaginal hemorrhage (n = 11), irregular menstruation (n = 6), and menstrual disorder (n = 4). The first two are consistent with the label; the latter two require further investigation.

3.3.1 Disease-Related Manifestations

As expected from the underlying pathophysiology of aTTP, the most frequently reported PTs in the FAERS database included diagnostic laboratory abnormalities and disease activity markers, namely decreased platelet count (n = 103), decreased ADAMTS13 activity (n = 98), TTP (n = 49), decreased hemoglobin (n = 40), and increased blood lactate dehydrogenase (n = 13) (Table 2). These PTs are consistent with the natural history of aTTP and were therefore excluded from the final list of drug-related AEs (see Section 2.3).

3.3.2 Drug-Related AEs and New Safety Signals

After excluding disease-related PTs and prescribing pattern indicators (product use in unapproved indication, n = 373), the most frequently reported plausible drug-related AEs were epistaxis (n = 100), contusion (n = 68), injection site pain (n = 56), injection site bruising (n = 50), gingival bleeding (n = 33), injection site erythema (n = 25), and injection site rash (n = 13) (Table 2). Epistaxis and gingival bleeding are consistent with the label and antithrombotic mechanism of caplacizumab. Newly identified safety signals not fully described in the prescribing information include contusion, injection site pain, injection site erythema, injection site bruising, and injection site rash.

Table 1. Clinical characteristics of caplacizumab AE reports from the FAERS database (Q1 2019 to Q1 2025).

Characteristics	Case numbers	Case proportion (%)
Number of events	1144	
Gender		
Male	279	24.40%
Female	662	57.90%
Miss	203	17.70%
Age		
<18	35	3.10%
18~65	689	60.20%
65~85	128	11.20%
>85	5	0.40%
missing	287	25.10%
Reported countries (Top 6)		
United States	973	85.10%
Germany	38	3.30%
France	33	2.90%
Italy	20	1.70%
Japan	14	1.20%
Israel	12	1.00%
Other countries and regions	54	4.80%
Outcome		
Death	55	4.80%
Disability	4	0.30%
Hospitalization	173	15.10%
Life-Threatening	8	0.70%
Other	904	79.00%
Reported type		
Consumer	580	50.70%
Health Professional	123	10.80%
Pharmacist	72	6.30%
Physician	353	30.90%
Missing	16	1.40%
Serious cases or NOT		
No	736	64.30%
Yes	408	35.70%
Fatal or NOT		
No	1089	95.20%
Yes	55	4.80%
GetData Year		
2019	103	9.00%
2020	162	14.20%
2021	202	17.70%
2022	217	19.00%
2023	201	17.60%
2024	196	17.10%
2025	63	5.50%

3.3.3 Prescribing Pattern Indicator

Product use in an unapproved indication was the most frequently reported PT (n = 373). As this reflects clinical practice patterns (e.g., the empiric initiation of caplacizumab before confirmatory ADAMTS13 testing due to the urgency of TTP treatment), it was not considered a drug-induced AE and was excluded from safety signal analysis.

3.4 Onset Times of Caplacizumab-Associated AEs

In total, 401 reports documenting the onset time of caplacizumab-associated AEs were collected. Most AEs occurred within 7 days after the initiation of caplacizumab treatment (n = 162, 40.4%; Fig. 5A), and those reported after one month of treatment had a share of 19.95%. According to Weibull distribution analysis, the median onset

Table 2. Caplacizumab-associated AEs at the PT level ranked by occurrence frequency.

PT	N	ROR (95% Cl)	PRR (χ^2)	EBGM (EBGM05)	IC (IC025)
Product use in an unapproved indication	373	17.87 (16.06–19.89)	16.19 (5338.61)	16.16 (14.52)	4.01 (3.8)
Platelet count decreased	103	16.26 (13.37–19.78)	15.84 (1431.57)	15.81 (13)	3.98 (3.5)
Epistaxis	100	25.76 (21.11–31.43)	25.1 (2308.29)	25.02 (20.5)	4.64 (4.05)
ADAMTS13 activity decreased	98	11,365.89 (8293.03–15,577.35)	11,069.44 (432,515.46)	4414.8 (3221.22)	12.11 (6.23)
Contusion	68	12.9 (10.14–16.4)	12.68 (731.53)	12.66 (9.96)	3.66 (3.09)
Injection site pain	56	3.49 (2.68–4.54)	3.45 (97.93)	3.45 (2.65)	1.79 (1.34)
ADAMTS13 activity abnormal	52	48,392.63 (22,972.27–101,942.32)	47,722.85 (330,865.26)	6363.91 (3020.99)	12.64 (5.17)
Injection site bruising	50	13.47 (10.19–17.82)	13.31 (568.69)	13.29 (10.05)	3.73 (3.01)
Thrombotic thrombocytopenic purpura	49	444.51 (332.6–594.08)	438.73 (20,193.75)	414.05 (309.8)	8.69 (5.06)
Hospitalisation	45	4.14 (3.08–5.55)	4.1 (105.68)	4.1 (3.05)	2.03 (1.51)
Platelet count abnormal	45	111.45 (82.89–149.86)	110.13 (4794.86)	108.52 (80.7)	6.76 (4.59)
Haemoglobin decreased	40	7.45 (5.46–10.18)	7.38 (220.85)	7.38 (5.4)	2.88 (2.22)
Platelet count increased	36	43.84 (31.54–60.93)	43.43 (1483.84)	43.18 (31.07)	5.43 (3.86)
Haemorrhage	34	5.82 (4.15–8.16)	5.78 (134.49)	5.78 (4.12)	2.53 (1.85)
Gingival bleeding	33	42.72 (30.29–60.24)	42.35 (1324.97)	42.11 (29.86)	5.4 (3.75)
Injection site erythema	25	5.13 (3.46–7.6)	5.1 (82.53)	5.1 (3.44)	2.35 (1.57)
Injection site haemorrhage	24	5.21 (3.49–7.78)	5.18 (81.01)	5.18 (3.47)	2.37 (1.57)
Gastrointestinal haemorrhage	22	6.01 (3.95–9.14)	5.98 (91.2)	5.97 (3.93)	2.58 (1.69)
Injection site pruritus	19	6.52 (4.16–10.24)	6.5 (88.36)	6.49 (4.14)	2.7 (1.7)
Heavy menstrual bleeding	16	13.18 (8.06–21.54)	13.13 (178.96)	13.1 (8.02)	3.71 (2.23)
Unevaluable event	15	3.79 (2.28–6.29)	3.78 (30.62)	3.77 (2.27)	1.92 (0.96)
Haematocrit decreased	15	17.14 (10.32–28.47)	17.07 (226.52)	17.04 (10.25)	4.09 (2.36)
Haemoglobin abnormal	15	36.9 (22.2–61.35)	36.76 (519.25)	36.58 (22)	5.19 (2.78)
Laboratory test abnormal	14	8.37 (4.95–14.16)	8.35 (90.46)	8.34 (4.93)	3.06 (1.74)
Injection site rash	13	8.5 (4.93–14.65)	8.47 (85.58)	8.46 (4.91)	3.08 (1.69)
Blood lactate dehydrogenase increased	13	19.8 (11.48–34.15)	19.73 (230.6)	19.68 (11.41)	4.3 (2.3)
Vaginal haemorrhage	11	6.01 (3.33–10.87)	6 (45.8)	5.99 (3.32)	2.58 (1.25)
Rectal haemorrhage	11	5.05 (2.79–9.13)	5.04 (35.62)	5.04 (2.79)	2.33 (1.08)
Mood altered	9	6.91 (3.59–13.29)	6.89 (45.32)	6.89 (3.58)	2.78 (1.2)
Haematocrit abnormal	9	116 (60–224.26)	115.72 (1007.72)	113.94 (58.94)	6.83 (2.29)
White blood cell count abnormal	9	19.25 (10–37.06)	19.21 (154.96)	19.16 (9.95)	4.26 (1.85)
Red blood cell count decreased	9	5.08 (2.64–9.77)	5.07 (29.38)	5.06 (2.63)	2.34 (0.93)
Blood lactate dehydrogenase abnormal	9	234.05 (120.44–454.84)	233.49 (2019.26)	226.32 (116.46)	7.82 (2.34)
Red blood cell count abnormal	9	85.35 (44.21–164.79)	85.15 (739.91)	84.19 (43.6)	6.4 (2.26)
Incorrect route of product administration	9	4.89 (2.54–9.4)	4.88 (27.74)	4.87 (2.53)	2.29 (0.9)
Catheter site haemorrhage	7	51.69 (24.56–108.79)	51.6 (344.93)	51.25 (24.35)	5.68 (1.79)
Mean cell volume abnormal	7	286.05 (134.35–609.07)	285.52 (1910.39)	274.87 (129.09)	8.1 (1.92)

Table 2. Continued.

PT	N	ROR (95%CI)	PRR(χ^2)	EBGM (EBGM05)	IC (IC025)
Haematoma	6	4.68 (2.1–10.44)	4.68 (17.34)	4.68 (2.1)	2.23 (0.52)
Menstruation irregular	6	9.62 (4.32–21.44)	9.61 (46.21)	9.59 (4.31)	3.26 (1.01)
Troponin increased	6	12.96 (5.81–28.89)	12.94 (66)	12.92 (5.8)	3.69 (1.16)
Injection site discolouration	6	10.42 (4.68–23.22)	10.4 (50.94)	10.39 (4.66)	3.38 (1.06)
Petechiae	5	9.52 (3.96–22.9)	9.51 (38.03)	9.5 (3.95)	3.25 (0.79)
Red cell distribution width increased	5	15 (6.23–36.08)	14.98 (65.09)	14.95 (6.21)	3.9 (0.99)
Injection site irritation	5	11.88 (4.94–28.58)	11.86 (49.67)	11.85 (4.92)	3.57 (0.9)
Dialysis	4	6.46 (2.42–17.23)	6.45 (18.42)	6.45 (2.42)	2.69 (0.33)
Thrombocytosis	4	17.13 (6.42–45.72)	17.11 (60.55)	17.08 (6.4)	4.09 (0.72)
Transfusion	4	6.58 (2.47–17.56)	6.58 (18.91)	6.57 (2.46)	2.72 (0.34)
Mouth haemorrhage	4	9.89 (3.71–26.39)	9.88 (31.89)	9.87 (3.7)	3.3 (0.54)
Menstrual disorder	4	10.39 (3.9–27.73)	10.38 (33.88)	10.37 (3.89)	3.37 (0.56)
Subarachnoid haemorrhage	4	7.15 (2.68–19.06)	7.14 (21.1)	7.13 (2.67)	2.83 (0.39)
Red cell distribution width abnormal	4	288.23 (106.08–783.12)	287.92 (1100.54)	277.09 (101.98)	8.11 (0.98)
Product preparation issue	4	6.64 (2.49–17.7)	6.63 (19.12)	6.63 (2.48)	2.73 (0.35)
Mean cell haemoglobin concentration abnormal	4	345.87 (126.82–943.29)	345.5 (1312.28)	330.02 (121.01)	8.37 (0.98)
ADAMTS13 activity increased	4	9799.73 (2192.49–43,801.67)	9789.3 (16,778.24)	4195.99 (938.77)	12.03 (0.67)
Pulmonary alveolar haemorrhage	4	11.5 (4.31–30.67)	11.49 (38.23)	11.47 (4.3)	3.52 (0.6)
Neutrophil count abnormal	4	21.4 (8.01–57.12)	21.37 (77.46)	21.31 (7.98)	4.41 (0.78)
Product administered to a patient of an inappropriate age	4	6.2 (2.32–16.53)	6.19 (17.4)	6.19 (2.32)	2.63 (0.31)
Neutrophil count increased	4	7.12 (2.67–18.99)	7.11 (21)	7.11 (2.67)	2.83 (0.39)
Hemiplegia	3	7.65 (2.47–23.75)	7.65 (17.32)	7.64 (2.46)	2.93 (0.08)
Gingival pain	3	7.8 (2.51–24.22)	7.8 (17.76)	7.79 (2.51)	2.96 (0.09)
Haemolysis	3	7.81 (2.52–24.23)	7.8 (17.77)	7.8 (2.51)	2.96 (0.09)
Fibrin d dimer increased	3	13.82 (4.45–42.91)	13.81 (35.58)	13.79 (4.44)	3.79 (0.27)
Intestinal haemorrhage	3	10.19 (3.28–31.64)	10.18 (24.81)	10.17 (3.28)	3.35 (0.18)
Granulocytes abnormal	3	293.91 (92.65–932.38)	293.68 (841.39)	282.42 (89.03)	8.14 (0.51)
Product reconstitution quality issue	3	39.01 (12.54–121.39)	38.98 (110.44)	38.78 (12.47)	5.28 (0.44)
Mean platelet volume decreased	3	46.8 (15.03–145.7)	46.76 (133.51)	46.47 (14.93)	5.54 (0.46)
Reticulocyte count increased	3	71.57 (22.95–223.23)	71.51 (206.57)	70.83 (22.71)	6.15 (0.49)
Infusion site haemorrhage	3	11.69 (3.76–36.29)	11.68 (29.25)	11.66 (3.76)	3.54 (0.22)
Von Willebrand's factor activity decreased	3	2449.28 (662.81–9050.79)	2447.33 (5501.99)	1835.74 (496.78)	10.84 (0.35)
Mean cell volume increased	3	16.2 (5.21–50.3)	16.18 (42.64)	16.15 (5.2)	4.01 (0.31)
Mean cell haemoglobin increased	3	22.87 (7.36–71.06)	22.85 (62.48)	22.78 (7.33)	4.51 (0.37)
Heparin–induced thrombocytopenia	3	14.32 (4.61–44.48)	14.31 (37.07)	14.29 (4.6)	3.84 (0.28)

PT, Preferred term; N, number of cases; ROR, reporting odds ratio; CI, confidence interval.

Note: Part of these PTs reflect underlying disease activity rather than drug-induced AEs.

time for caplacizumab-related AEs was 10 days (interquartile range (IQR) = 1–1469 days), and the distribution parameters are shown in Fig. 5B.

3.5 PT Analysis in Subgroups

We conducted PT analyses in subgroups based on gender, age, and reporter type. Both male and female patients had significantly higher reporting frequencies of unapproved product use relative to all other PTs (Fig. 6A). This high frequency reflects the diagnostic challenge of aTTP, the delayed availability of ADAMTS13 testing, and the need for urgent treatment initiation rather than the incomplete understanding of labeled indications. Additionally, compared with other PTs, men more frequently reported decreased platelet count, decreased/abnormal ADAMTS13 activity, and epistaxis, while women were more prone to report fatigue, epistaxis, decreased ADAMTS13 activity, and decreased platelet count. Individuals under 18 were more likely to experience off-label use and product use in unapproved indications, those aged 18–65 more frequently reported product use in unapproved indications, epistaxis, fatigue, decreased ADAMTS13 activity, decreased platelet count, headache, contusion, etc., and those over 65 often experienced product use in unapproved indications, de-

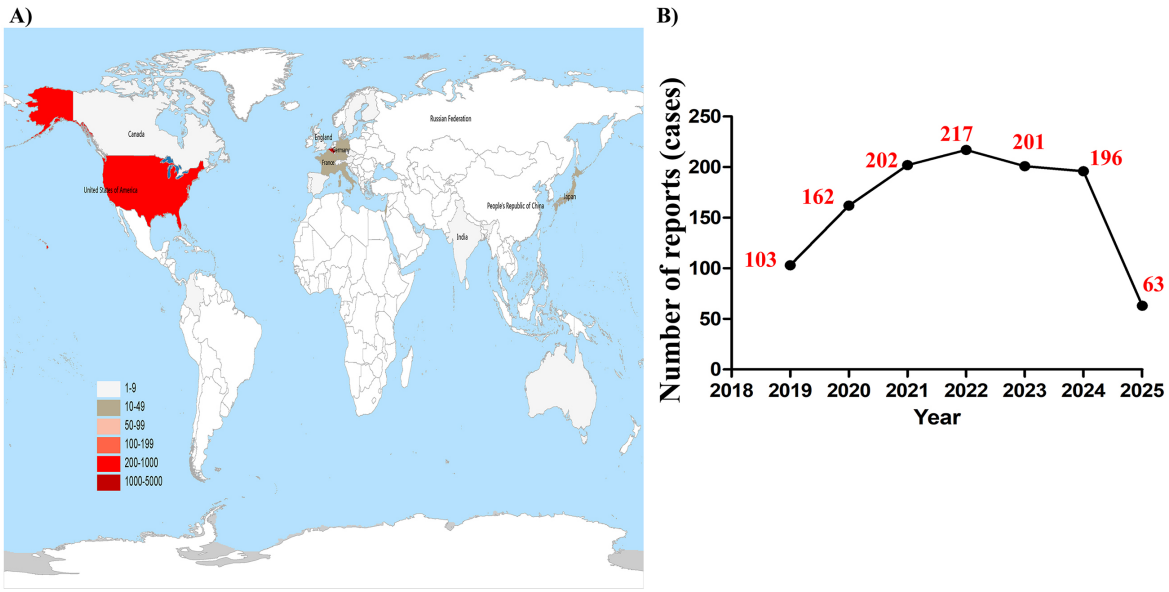


Fig. 2. Spatiotemporal distribution of reported cases. (A) Global geographic distribution of reported cases, with the range of cumulative reported cases per country indicated by color: white (1–9 cases), light brown (10–49 cases), light orange (50–99 cases), orange (100–199 cases), red (200–1000 cases), and dark red (1000–5000 cases). (B) Temporal trend of reported cases in 2019–2025.

System Organ Class (SOC)	Case number	ROR (95%CI)
Investigations	761	4.16 (3.84, 4.50)
Injury, poisoning and procedural complications	723	1.68 (1.55, 1.82)
Respiratory, thoracic and mediastinal disorders	197	1.16 (1.01, 1.34)
Blood and lymphatic system disorders	108	1.72 (1.42, 2.08)
Vascular disorders	98	1.42 (1.16, 1.73)
Surgical and medical procedures	73	1.31 (1.04, 1.65)
Reproductive system and breast disorders	48	1.99 (1.50, 2.65)

Fig. 3. Forest plot of caplacizumab-associated AEs at the system organ class (SOC) level. ROR (reporting odds ratio) was calculated for signal detection. A positive signal was defined as a lower limit of 95% CI >1 with n ≥ 3. Note: The ROR value itself is not an absolute measure of clinical risk.

creased platelet count, decreased ADAMTS13 activity, decreased hemoglobin, TTP, aggravated conditions, epistaxis, etc. (Fig. 6B). Consumers, health professionals, and physicians were most prone to report product use in unapproved indications, while pharmacists tended to be most aware of decreased platelet count (Fig. 6C). Additionally, consumers were more likely to report epistaxis, fatigue, contusion, and off-label use. Health professionals were more likely to report decreased/abnormal ADAMTS13 activity, off-label use, decreased platelet count, decreased hemoglobin, and epistaxis, while physicians more frequently reported off-label use, decreased platelet count, decreased ADAMTS13 activity, and TTP. Pharmacists were more aware of off-label use, hemorrhage, epistaxis, and injection site pain.

3.6 Onset Time Analysis in Subgroups

We also conducted subgroup analyses of onset time according to gender, age, and reporter type. The onset time of caplacizumab-induced AEs was defined as the interval between the time of the first administration and the time when the first symptoms appeared. In the gender subgroup (Fig. 7A), the median onset times for males and females were 9 days (IQR = 1–1469 days) and 12 days (IQR = 1–743 days), respectively. In the age group (Fig. 7B), the median

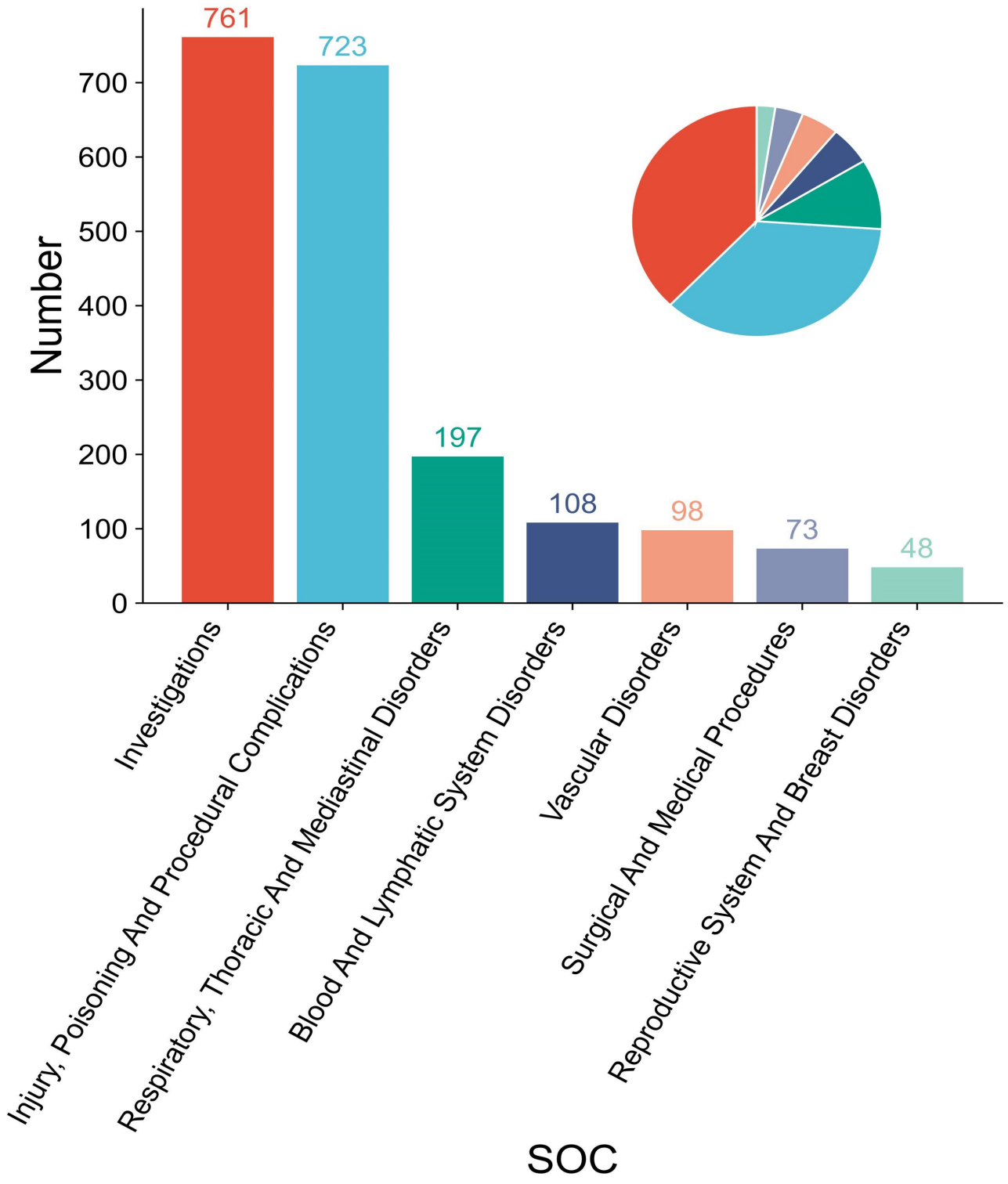


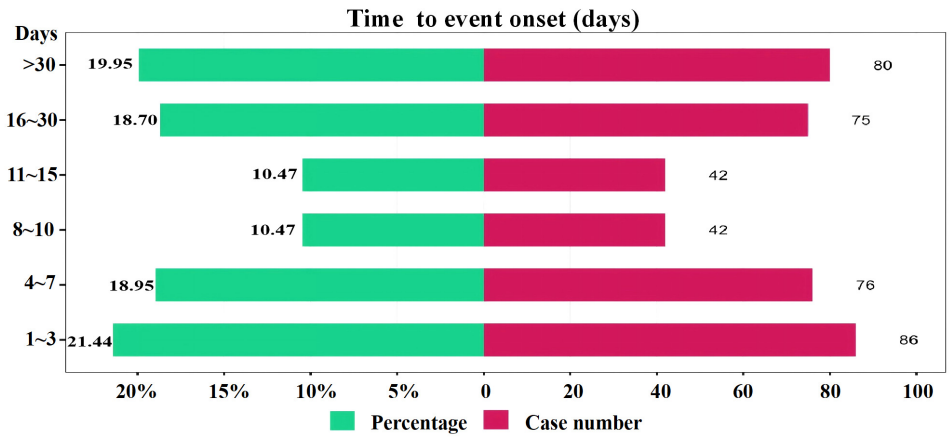
Fig. 4. Caplacizumab-associated AEs at the SOC level.

onset times for adults aged 18–65 and >65 were 16 days (IQR = 1–1469 days) and 6 days (IQR = 1–743), respectively. In the reporter subgroup (Fig. 7C), the median onset times for consumers, health professionals, physicians, and pharmacists were 12 days (IQR = 1–1469 days), 18 days (IQR = 1–656 days), 5 days (IQR = 1–743 days), and 16 days (IQR = 1–119 days), respectively. Other relevant parameters can be found in Fig. 7.

4. Discussion

aTTP is a rare life-threatening autoimmune thrombotic microangiopathy with an annual prevalence of 10

A)



B)

Drug	TTO (days)		Weibull distribution		
	Case reports	Median(d) (IQR)	Scale parameter: α(95%CI)	Shape parameter: β(95%CI)	Type
Caplacizumab	401	10(1-1469)	22.50(18.60-26.39)	0.60(0.56-0.64)	Early failure

Fig. 5. Onset time of caplacizumab-related AEs. (A) Distribution of onset time categories and (B) Weibull distribution analysis of onset time. IQR, interquartile range.

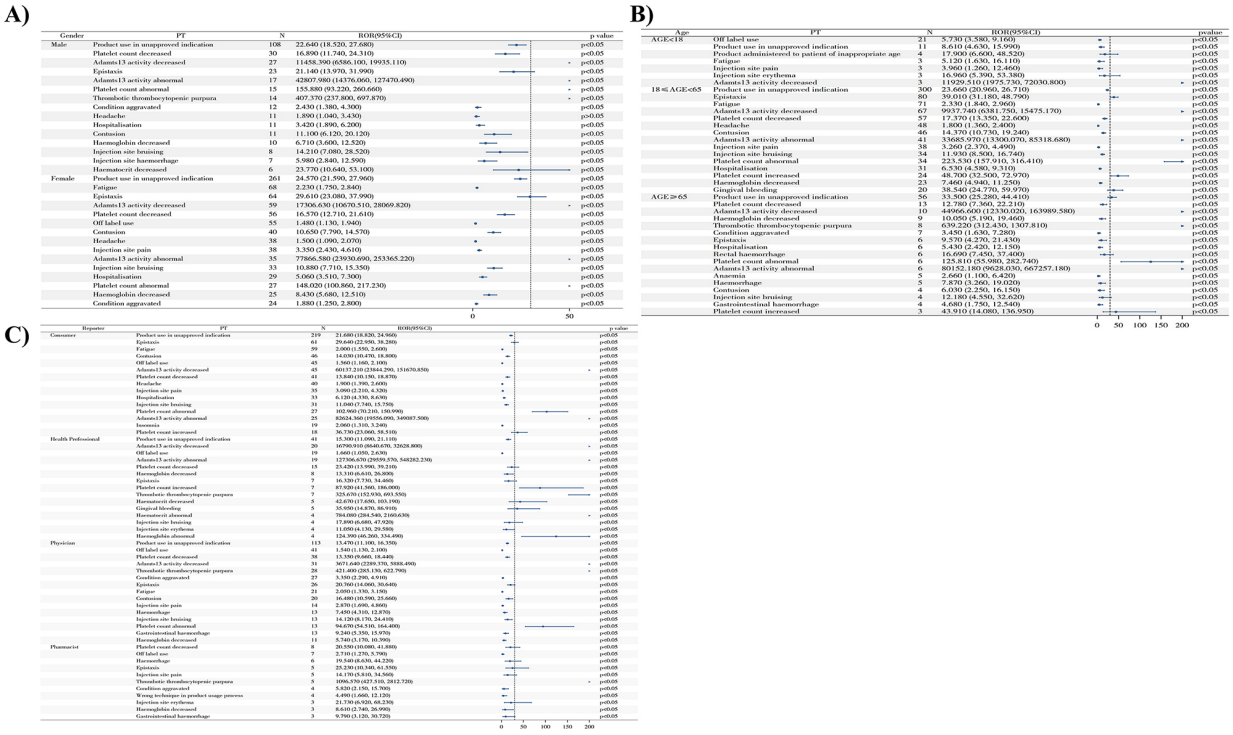


Fig. 6. Subgroup analysis of disproportionality signals by different demographic and reporter groups. Forest plots showing the RORs and 95% CIs for AEs stratified by (A) gender, (B) age, and (C) reporter type. Statistical significance was set at $p < 0.05$.

cases per million [14]. Plasma exchange combined with immunosuppression is the standard treatment, although some patients do not respond adequately [2]. Caplacizumab, a nanobody inhibiting vWF–platelet interactions, has shown efficacy in reducing the time to platelet response and improving outcomes [15,16].

A) Male

Drug	TTO (days)		Weibull distribution		
	Case reports	Median(d) (IQR)	Scale parameter: α(95%CI)	Shape parameter: β(95%CI)	Type
Caplacizumab	71	9(1-1469)	38.64(17.02-60.27)	0.45(0.37-0.52)	Early failure

Female

Drug	TTO (days)		Weibull distribution		
	Case reports	Median(d) (IQR)	Scale parameter: α(95%CI)	Shape parameter: β(95%CI)	Type
Caplacizumab	267	12(1-743)	19.30(15.87-22.72)	0.75(0.69-0.82)	Early failure

B) Age 18~65

Drug	TTO (days)		Weibull distribution		
	Case reports	Median(d) (IQR)	Scale parameter: α(95%CI)	Shape parameter: β(95%CI)	Type
Caplacizumab	235	16(1-1469)	32.31(25.00-39.63)	0.60(0.55-0.65)	Early failure

Age >65

Drug	TTO (days)		Weibull distribution		
	Case reports	Median(d) (IQR)	Scale parameter: α(95%CI)	Shape parameter: β(95%CI)	Type
Caplacizumab	96	6(1-743)	8.53(5.65-11.40)	0.63(0.55-0.71)	Early failure

C) Consumer

Drug	TTO (days)		Weibull distribution		
	Case reports	Median(d) (IQR)	Scale parameter: α(95%CI)	Shape parameter: β(95%CI)	Type
Caplacizumab	161	12(1-1469)	34.25(24.64-43.86)	0.59(0.53-0.65)	Early failure

Health professional

Drug	TTO (days)		Weibull distribution		
	Case reports	Median(d) (IQR)	Scale parameter: α(95%CI)	Shape parameter: β(95%CI)	Type
Caplacizumab	50	18(1-656)	41.30(24.73-57.81)	0.74(0.59-0.89)	Early failure

Physician

Drug	TTO (days)		Weibull distribution		
	Case reports	Median(d) (IQR)	Scale parameter: α(95%CI)	Shape parameter: β(95%CI)	Type
Caplacizumab	160	5(1-743)	10.41(7.74-13.07)	0.64(0.58-0.71)	Early failure

Pharmacist

Drug	TTO (days)		Weibull distribution		
	Case reports	Median(d) (IQR)	Scale parameter: α(95%CI)	Shape parameter: β(95%CI)	Type
Caplacizumab	22	16(1-119)	22.51(11.64-33.38)	0.93(0.63-1.24)	Early failure

Fig. 7. Onset times of caplacizumab-related AEs and corresponding Weibull distribution analysis in (A) gender, (B) age, and (C) reporter subgroups. TTO, time to onset; CI, confidence interval; IQR, interquartile range.

4.1 Overall Distribution of AEs

The demographic distribution of AEs (57.9% female, 60.2% aged 18–65 years) mirrors the known epidemiology of aTTP, which predominates in adult women (female-to-male ratio = 2.5–3.5) [17]. This pattern reflects the target patient population rather than a differential safety profile of caplacizumab. Most reports originated from the United States (85.1%), probably because FAERS is an FDA-established system with a relatively mature pharmacovigilance framework encouraging comprehensive AE reporting [18]. Although the mortality rate was low (4.8%), the proportion of prolonged hospital stays (15.1%) suggests that caplacizumab-related AEs may impact healthcare utilization. Consumers (50.7%) and physicians (30.9%) were the primary reporters, which reflects the fact that patients directly experience AEs while physicians provide professional verification. The low proportion of serious or fatal events indicates that caplacizumab is relatively safe, although vigilance for potential AEs remains warranted.

4.2 Distribution of AEs Signals at the SOC Level

At the SOC level, investigations had the highest frequency of reports and signal intensity, possibly because the action mechanism of caplacizumab, which targets vWF–platelet interactions, may lead to changes in laboratory parameters that are frequently monitored in clinical practice. For example, it may affect platelet-related indices, coagulation factors, or markers of hemolysis, thus triggering more laboratory investigations [19].

When disaggregated into PTs, most reports in the reproductive system and breast disorders SOC were heavy menstrual bleeding and vaginal hemorrhage, which align with the antithrombotic mechanism of caplacizumab and are already noted in the product label. We also identified less common PTs, including irregular menstruation (n = 6) and menstrual disorder (n = 4). Although these can reflect disease-related hormonal disturbances or the physiological stress of acute illness, they may also represent underrecognized effects of caplacizumab. Given the limited number of cases, these signals should be interpreted cautiously and investigated further.

4.3 Distinguishing Drug-Related AEs From Disease-Related Manifestations

As detailed in Section 3.3.1, several frequently reported PTs—including decreased platelet count, decreased ADAMTS13 activity, TTP, decreased hemoglobin, and increased Lactate Dehydrogenase (LDH)—are established diagnostic markers of aTTP rather than drug-induced AEs. Mechanistically, caplacizumab inhibits vWF–platelet interactions, reducing platelet adhesion and consumption [20], and is therefore expected to increase platelet count rather than decrease it [3]. Reports of thrombocytopenia during treatment more likely reflect refractory or relapsing disease, incomplete response to plasma exchange, or confounding factors (e.g., infection or concomitant medications) [21]. Similarly, persistently low ADAMTS13 activity indicates ongoing autoimmune activity and predicts clinical relapse [22,23]. A French cohort study showed that among 23

aTTP patients in remission with ADAMTS13 activity of <10%, the recurrence rate reached 74% at 7 years [24]. Our findings are consistent with those of the Capla 1000+ study, which did not list decreased platelet count or ADAMTS13 activity as AEs, corroborating our reclassification of these as disease-related manifestations rather than drug-induced AEs [13]. After excluding disease-related PTs, the plausible drug-related AEs were bleeding events (epistaxis, gingival bleeding, gastrointestinal hemorrhage, heavy menstrual bleeding, vaginal hemorrhage) consistent with the product label [25,26], and injection site reactions (pain, erythema, bruising, rash) plus contusion as newly identified safety signals. These injection site findings align with the real-world report of Jiménez et al. [27], where 2 of 10 patients experienced local inflammatory reactions.

Product use in unapproved indications, the most frequently reported PT, reflects the clinical challenge of initiating urgent TTP treatment before confirmatory ADAMTS13 results are available, not a drug safety concern. The observed prolonged hospital stay in some reports appears inconsistent with clinical trials showing shorter hospitalization with caplacizumab [2,28] and requires cautious interpretation because of the lack of detailed clinical data.

In summary, disease-related manifestations should be carefully distinguished from true AEs for the accurate safety profiling of caplacizumab. Our findings highlight injection site reactions and contusion as real-world safety signals, while abnormalities in platelet count and ADAMTS13 activity should be interpreted in the context of aTTP activity.

4.4 Onset Time of AEs

Most AEs (40.4%) occurred within 7 days after the initiation of caplacizumab treatment, with the median onset time determined as 10 days. This relatively short onset time suggests that most AEs associated with caplacizumab can be detected early in the treatment process. Early-onset AEs may be related to the immediate impact of the drug on the vWF–platelet interaction pathway, leading to changes in platelet function and coagulation status. For example, the rapid binding of caplacizumab to vWF may trigger an immediate response in the body's hemostatic system, resulting in bleeding-related AEs such as epistaxis or contusion. The high proportion of early AEs emphasizes the importance of closely monitoring patients in the initial days of caplacizumab treatment.

4.5 Subgroup Analysis of AEs

Both men and women had a high frequency of product use in unapproved indications. This high frequency probably reflects the clinical urgency in treating suspected TTP. As ADAMTS13 activity assays are not universally available as point-of-care tests, clinicians often initiate caplacizumab treatment empirically based on clinical criteria to avoid treatment delays, which leads to reports of off-label use before diagnostic confirmation. Men more frequently reported laboratory abnormalities reflecting disease activity (decreased platelet count, decreased/abnormal ADAMTS13 activity) and epistaxis, while women were more prone to report fatigue and epistaxis. The higher proportion of AE reports for women (57.9%) is largely explained by two factors. First, aTTP itself has a female predominance (female-to-male ratio = 2.5–3.5) [17]. Second, gynecological bleeding events (heavy menstrual bleeding, n = 16; vaginal hemorrhage, n = 11) account for a substantial proportion of reported AEs in women, which is consistent with the antithrombotic mechanism of caplacizumab. Thus, the female predominance reflects disease epidemiology and the specific manifestation of bleeding in the gynecological tract, not an intrinsic gender difference in drug safety [29].

Different age groups showed distinct AE patterns. Patients under 18 featured more pronounced off-label use, probably because of limited pediatric studies. Adults aged 18–65 most frequently reported off-label use, epistaxis, fatigue, and decreased ADAMTS13/platelet count. Those over 65 additionally reported decreased hemoglobin and TTP. Age-related changes in drug metabolism and clearance may contribute to these differences [23,30,31].

Consumers, health professionals, and physicians most frequently reported off-label use, while pharmacists were more aware of decreased platelet count. Consumers preferentially reported epistaxis, fatigue, and contusion, which reflects direct symptom experience. Health professionals and physicians more often reported decreased ADAMTS13 activity and platelet count, whereas pharmacists were more attentive to hemorrhage, epistaxis, and injection site pain, which is consistent with their medication counseling role.

4.6 Limitations

The FAERS database is a spontaneous reporting system, which means that the data may be incomplete, inaccurate, or subject to underreporting. Some AEs may not be reported, and the reported events may lack detailed information, which may affect analysis accuracy [32]. The causal relationship between caplacizumab and the reported AEs cannot be firmly established based on the data in this database alone, as confounding factors (e.g., concomitant medications or underlying diseases) may contribute to AE occurrence [33]. The data in the FAERS database do not distinguish between different caplacizumab dosages and treatment durations, which makes the dose–response relationship of these AEs difficult to analyze. Although we have provided granular PT-level analyses for SOCs of interest (e.g., reproductive disorders and fatal events), the spontaneous nature of FAERS data means that some reports lack sufficient clinical detail for complete case ascertainment, particularly for cause-of-death attribution (47.3% of fatal cases had undocumented causes). The FAERS database lacks denominator data on the total number of patients ex-

posed to caplacizumab, which precludes the calculation of true AE incidence rates. Based on the Capla 1000+ study, which included 1015 treated patients from 2018–2023 [13], the global treated population during our study period probably exceeds 2000–3000 patients, providing context for the 1144 reports analyzed.

5. Conclusion

This real-world pharmacovigilance study based on the FAERS database provides valuable insights into the safety profile of caplacizumab. A variety of caplacizumab-associated AEs were identified, some of which were consistent with the label, such as epistaxis, gingival bleeding, gastrointestinal hemorrhage, heavy menstrual bleeding, and vaginal hemorrhage. Bleeding-related events and injection site reactions (e.g., contusion, pain, bruising, erythema, haemorrhage, pruritus and rash) were identified as new real-world safety signals. Decreased platelet count and decreased ADAMTS13 activity are aTTP-related manifestations, not AEs of caplacizumab. Most AEs were found to occur early in the treatment process, which emphasizes the need for close initial monitoring. Subgroup analysis revealed differences in AEs among different genders, ages, and reporter types. These findings can help healthcare providers make more informed decisions when prescribing caplacizumab and contribute to the continuous improvement of its safety monitoring and management. Future studies, such as well-designed observational studies and clinical trials, are needed to confirm and expand on these findings and ensure the rational and safe use of caplacizumab in the treatment of aTTP.

Availability of Data and Materials

The data analyzed in this study were obtained from the publicly available US FDA Adverse Event Reporting System (FAERS) database (https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard). The database is open access and freely available to the public. The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

JS, JL, HX and XY contributed to the study conception and design. Material preparation, data collection and analysis were performed by JL and HX. The first draft of the manuscript was written by JS and revised by HX, and XY. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was conducted based on a publicly available, de-identified adverse event database (FAERS). Since no individual patient-level identifiable information or human participants were involved, ethics approval and informed consent were not applicable for this retrospective pharmacovigilance study.

Acknowledgment

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/Pharmazie52100.

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