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Coagulation dysfunction events associated with echinocandins: a real-world study from FDA adverse event reporting system (FAERS) database

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Abstract

Background Echinocandins belong to the fourth generation of antifungals, and there are no systematic studies on their risk in coagulation dysfunction; this study will predict the risk of coagulation dysfunction of echinocandins using the US Food and Drug Administration Adverse Event Reporting System (FAERS) database.

Method Data from January 2004 to March 2024 were obtained from FAERS. We examined the clinical characteristics of the coagulation dysfunction events and conducted disproportionality analysis by using reporting odds ratios (ROR) to compare echinocandins with the full database.

Results There were 313 reports of coagulation dysfunction related to echinocandins as the primary suspect (PS) drug. The median time to incident for coagulation dysfunction was 3 (interquartile range [IQR] 1–9) days. Compared to triazoles and polyenes, echinocandins have a stronger signal (ROR 3.18, 95%CI 2.81–3.51, $p < 0.01$) of coagulation dysfunction. Compared to caspofungin and micafungin, anidulafungin has a stronger signal (ROR 6.84, 95%CI 4.83–9.70, $p < 0.01$). The strongest signal corresponding to disseminated intravascular coagulation (DIC), platelet count decreased, thrombocytopenia, gastrointestinal haemorrhage, cerebral haemorrhage, pulmonary haemorrhage and thrombotic thrombocytopenic purpura (TTP) is micafungin (ROR 27.19, 95%CI 18.49–39.98), micafungin (ROR 3.50, 95%CI 2.36–5.19), anidulafungin (ROR 9.75, 95%CI 5.22–18.19), micafungin (ROR 3.17, 95%CI 2.02–4.97), micafungin (ROR 4.95, 95%CI 2.81–8.72), caspofungin (ROR 20.76, 95%CI 11.77–36.59), micafungin (ROR 20.43, 95%CI 8.49–49.14), respectively.

Conclusions For coagulation dysfunction, we found stronger signals for echinocandins than triazoles and polyenes, and stronger signals for anidulafungin than micafungin and caspofungin. Coagulation parameters should be closely monitored while using the respective drugs.

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Highlights

- Real world data were used to predict the risk of coagulopathy for three classes of drugs: echinocandins, triazoles, and polyenes.
- Real-world data were used to compare the risk of coagulopathy between caspofungin, micafungin, and anidulafungin.
- Different causes of coagulation dysfunction were analyzed by subgroups.

Keywords Caspofungin, Micafungin, Anidulafungin, Coagulation dysfunction, FAERS, Pharmacovigilance

Background

Fungal infections have a high morbidity and mortality rate and pose a serious threat to human health [1]. Commonly used antifungal drugs include echinocandins, triazoles and polyenes. Echinocandins belong to the fourth generation of antifungal drugs. FDA-approved echinocandins include caspofungin, micafungin, anidulafungin, and rezafungin. These drugs have demonstrated significant antifungal efficacy through the specific inhibition of β-(1,3) -D-glucan synthesis, which forms 30–60% of the fungal cell wall [2–6]. All of them can be used as anti-infective therapy for *Candida*, and caspofungin is approved for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies [7].

The main adverse events (AEs) of echinocandins in premarketing studies were elevated alanine aminotransferase (ALT), elevated aspartate aminotransferase (AST), fever, phlebitis, gastrointestinal reactions, headache and rash [8–11]. Meanwhile, thrombocytopenia has been reported in clinical trials of micafungin and anifungin [9, 10]. DIC has also been reported in clinical trials of rezafungin [11]. However, there are few post-marketing studies on coagulation dysfunction caused by echinocandins. This study will use real-world data from the FAERS database to explore the risk of coagulopathy with echinomycin for clinicians to reference.

Methods

Study design and data sources

The target drugs in this study include caspofungin, micafungin, and anidulafungin (rezafungin has no reported AEs related to coagulation dysfunction due to a marketing date of 2023.03.22). Control drugs included voriconazole, itraconazole, fluconazole, posaconazole, isavuconazonium, and amphotericin B. This study included all records in the FAERS database from January 2004 to March 2024 (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html). Generic and brand names were employed to define target/control drugs (supplementary Table 1). Reports in the DRUG table where role_code is "primary suspect" were included in the study.

We define coagulation dysfunction events through the preferred terms (PT) level in the Medical Dictionary for Regulatory Activities terms (MeDRA V25.1). The specific list is shown in supplementary Table 2. The primary outcome was overall coagulation-related AEs. The secondary outcomes comprised the reporting of coagulation dysfunction events with a high frequency: DIC, platelet count decreased, thrombocytopenia, gastrointestinal haemorrhage, cerebral haemorrhage, pulmonary haemorrhage, TTP Table 1 and 2

Statistical analysis

In the disproportionality analyses, a positive signal occurs when there may be a significant correlation between the target AEs and the target drugs. In our study, ROR was used to calculate the signal strength of AEs. The ROR calculates the signal strength of a target drug by comparing the frequency of a target AE with background data. In this study, caspofungin, micafungin and anidulafungin were the target drugs and coagulopathy related events were the target AEs. A significant correlation between the target drugs and the target AEs was considered to exist when the following conditions were met: lower limit of the 95% CI is greater than 1, and number of reports is greater than 3. If one of the two conditions is not met, the correlation is considered insignificant (supplementary Table 3). Navicat Premium (16.0.1.2) and Graph Pad Prism (10.1.1) were used for data extraction and analysis. Pearson's chi-square test was used for statistical analysis and $p<0.05$ indicated that the results were statistically significant.

Robustness analysis (primary outcome)

To verify the robustness of the results, we performed four comparisons: (1) Coagulation dysfunction signal strength was calculated separately for 9 drugs (including 3 target drugs and 6 control drugs); (2) Total signal strength of coagulation dysfunction was calculated separately for echinocandins, polyenes, and triazoles; (3) Pearson's chi-square test was used to compare other drugs with amphotericin B and anidulafungin, respectively, to determine whether there were significant differences in signal strength between them. (4) Re-calculating the ROR (95%CI) after excluding consumer source reports.

Table 1 Clinical characteristics of patients with echinocandins-associated coagulation dysfunction events

	No. of coagulation dysfunction events in echinocandins (%)	No. of other AEs in echinocandins (%)
Reports	313	4395
Gender		
Male	175 (55.91)	2300 (52.33)
Female	116 (37.06)	1538 (34.99)
Unknown	22 (7.03)	557 (12.67)
Age		
< 20	32 (10.22)	442 (10.06)
≥ 20 and < 40	32 (10.22)	475 (10.81)
≥ 40 and < 60	63 (20.13)	939 (21.37)
≥ 60	146 (46.65)	1325 (30.15)
Reporter		
Healthcare workers	242 (77.32)	3130 (71.22)
Non-health care workers	64 (20.45)	1154 (26.26)
Unknown	7 (2.24)	111 (2.53)
Year		
2021–2024	25 (7.99)	597 (13.58)
2016–2020	51 (16.29)	1497 (34.06)
2011–2015	89 (28.43)	1359 (30.92)
2004–2010	117 (37.38)	941 (21.41)
Outcome		
Death	167 (53.35)	1579 (35.93)
Life-threatening	71 (22.68)	365 (8.30)
Disability	17 (5.43)	51 (1.16)
Hospitalization	101 (32.27)	1128 (25.67)
Other serious	190 (60.70)	1848 (42.05)
Congenital Anomaly	0 (0)	3 (0.07)
Required intervention	1 (0.32)	12 (0.27)
Report countries (Top 3)	Japan 51 (16.29)	America 960 (21.84)
	China 30 (9.58)	Japan 480 (10.92)
	America 15 (4.79)	France 277 (6.30)
Indications (Top 3)	Prophylaxis 57 (18.21)	Fungal infection 596 (13.56)
	Febrile neutropenia 49 (15.65)	Febrile neutropenia 329 (7.49)
	Fungal infection 39 (12.46)	Bronchopulmonary aspergillosis 293 (6.67)
Onset time (Median [IQR] / d)	3 (1–8)	-

Table 2 Quartile of coagulopathy events with different antifungal drugs

Drugs Onset time (d)	Micafungin	Caspofungin	Anidulafungin	Voriconazole	Itraconazole	Fluconazole	Posaconazole	Isavuconazole	Amphotericin B
Median	4	2.5	0	7	9.5	6	7	5.5	4
The first quartile	1	0.25	0	2	2.25	2	1	2.25	1
The third quartile	9	7	10.5	20.75	40	13	27	10.25	10

Subgroup analysis (secondary outcomes)

Also, to further explore the correlation between each drug and secondary outcomes, we did subgroup analyses for secondary outcomes. These secondary outcomes mainly included DIC, platelet count decreased, thrombocytopenia, gastrointestinal haemorrhage, cerebral haemorrhage, pulmonary haemorrhage and TTP.

Time to onset and death outcome statistics

We measured the onset time of all coagulopathy events that may have been associated with target/control drugs included in the study. The median and quartiles of onset time were used as an indicator of the latency of response to AEs. At the same time, we counted the death outcomes of the included reports.

Results

Descriptive analysis

A total of 313 reports of the target drugs were associated with coagulation dysfunction (caspofungin 128, micafungin 161, anidulafungin 24). Interestingly, although micafungin has been on the market for a shorter time than caspofungin, more coagulopathy reports have been reported than caspofungin. Anidulafungin was marketed only a year later than micafungin, but there were far fewer reports related to coagulation dysfunction. Males accounted for a higher proportion of reports associated with coagulation dysfunction than females (55.91% vs. 37.06%), and 46.65% of them were in the age group above 60 years old. Age distribution trends were consistent across the three target drugs The most reported indication was prophylaxis (18.21%), followed by febrile neutropenia (15.65%) and fungal infection (12.46%). The outcomes of death and life-threatening were reported in 167 (53.35%) and 71 (22.68%) reports respectively. Of course, the high proportion of death and life-threatening outcomes could also be due to the progression of the disease itself. Most AEs were reported from Japan (16.29%), followed by China (9.58%), and America (4.79%). The period with the highest number of reports is 2004–2010 (37.38%), followed by 2011–2015 (28.43%), 2016–2020 (16.29%) and 2021–2024 (7.99%), respectively.

Signal strength of overall coagulation dysfunction events (primary outcome)

The signal strength of each drug in terms of coagulation dysfunction is shown in Fig. 1. All three target drugs and six control drugs showed positive signals. Among the echinocandins, anidulafungin had the highest signal strength (ROR 6.84, 95%CI: 4.83–9.70), followed by micafungin (ROR 4.19, 95%CI: 3.63–4.83), and the weakest was caspofungin (ROR 3.31, 95%CI: 2.83–3.87). Among the triazoles, fluconazole had the highest signal strength (ROR 2.36, 95%CI: 2.20–2.54) and the weakest was voriconazole (ROR 1.40, 95%CI: 1.28–1.53).

Among the three major classes of drugs, echinocandins still had the strongest signal (ROR 3.18, 95%CI: 2.87–3.51), followed by the polyene (ROR 2.02, 95%CI: 1.79–2.27), and the triazoles had the weakest signal (ROR 1.55, 95%CI: 1.48–1.63). (Fig. 1)

When comparing the other drugs with amphotericin B using Pearson's chi-square test, caspofungin, micafungin, anidulafungin and fluconazole had a stronger signal strength than amphotericin B in coagulation dysfunction ($p<0.01$), and the signal strength of isavuconazonium was weaker than that of amphotericin B ($p<0.01$). When compared to anidulafungin, micafungin was not statistically different ($p=0.33$), and all other drugs had weaker signal strength than anidulafungin ($p<0.01$). (Fig. 1)

In addition, we tested the reliability of the results by excluding reports from consumer sources for sensitivity analyses, the results of which are shown in supplementary Fig. 1. Despite the reduction in the number of reports in the sensitivity analyses, there was very little change in the final signal strength. The results of the sensitivity analyses were generally consistent with the original results, except for the comparison between voriconazole and amphotericin B.

Subgroup	Coagulation dysfunction events (Target drugs/full database)	Other events (Target drugs/full database)	Statistic1	P.x vs. amp	Statistic2	P.x vs. ani	ROR (95% CI)
Target drugs							
Caspofungin	161/595864	5626/68923297	20.64	< 0.01	4.97	< 0.05	3.31 (2.83 to 3.87)
Micafungin	194/592622	5304/67825864	55.88	< 0.01	0.94	0.33	4.19 (3.63 to 4.83)
Anidulafungin	33/429388	749/66648337	23.59	< 0.01	-	-	6.84 (4.83 to 9.70)
Echinocandins	**388/719634**	**11679/68793247**	**58.4**	**< 0.01**	**-**	**-**	**3.18 (2.87 to 3.51)**
Control drug							
Amphotericin B	273/621618	15011/68888046	-	-	23.59	< 0.01	2.02 (1.79 to 2.27)
Polyene	**273/621618**	**15011/68888046**	**-**	**-**	**23.59**	**< 0.01**	**2.02 (1.79 to 2.27)**
Control drugs							
Fluconazole	786/792126	28859/68703177	32.8	< 0.01	7.16	< 0.01	2.36 (2.20 to 2.54)
Itraconazole	204/682636	11113/68830995	0.01	0.92	22.26	< 0.01	1.85 (1.61 to 2.13)
Voriconazole	527/773128	33455/68717838	3.66	0.66	34.36	< 0.01	1.40 (1.28 to 1.53)
Posaconazole	152/622679	8382/65649438	0.001	0.98	21.89	< 0.01	1.91 (1.63 to 2.24)
Isavuconazonium	17/211729	2145/47386428	11.58	< 0.01	40.56	< 0.01	1.77 (1.10 to 2.86)
Triazoles	**1686/888574**	**83954/68550734**	**2.27**	**0.13**	**-**	**-**	**1.55 (1.48 to 1.63)**

P.x vs. amp. P-values representing other drugs compared to amphotericin B
P.x vs. ani. p value representing other drugs compared to anidulafungin

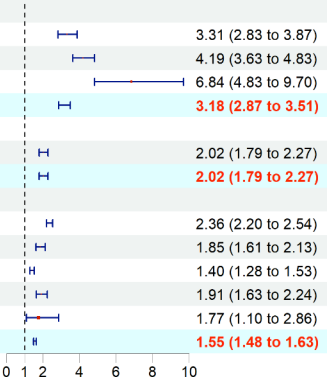

Fig. 1 Overall coagulation dysfunction signals and RORs comparing different drugs with the full database. (ROR reporting odds ratios, 95%CI 95% confidence interval)

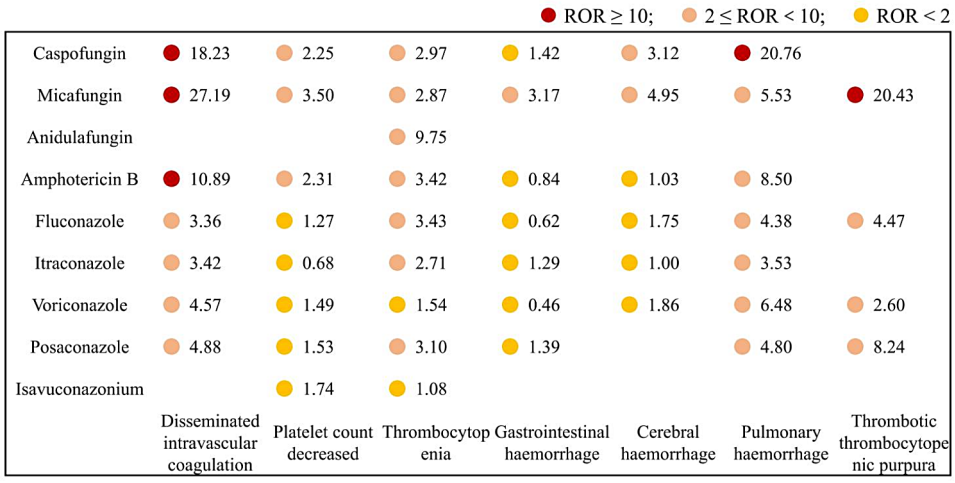

Fig. 2 Subgroup analysis of different coagulation dysfunction events in different drugs

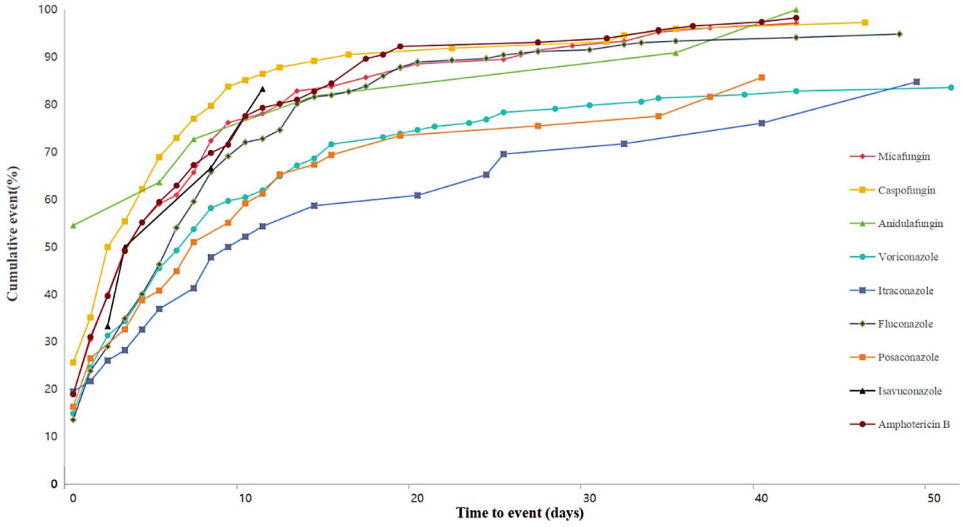

Fig. 3 Cumulative event (%) of coagulation events since the initiation of different drugs

Signal strength of different coagulation dysfunction events (secondary outcomes)

In terms of DIC, micafungin showed the strongest signal strength (ROR 27.19, 95%CI 18.49–39.98), followed by caspofungin (ROR 18.23, 95%CI 11.62–28.61) and amphotericin B (ROR 10.89, 95%CI 7.61–15.59). In terms of pulmonary haemorrhage, caspofungin had the highest signal strength (ROR 20.76, 95%CI 11.77–36.59), and for TTP, it was still micafungin that had the highest signal strength (ROR 20.43, 95%CI 8.49–49.14). It is worth noting that anidulafungin only showed a strong signal in thrombocytopenia (ROR 9.75, 95%CI 5.22–18.19). Other secondary outcome signals are mostly positive, but ROR values are generally below 10. (Fig. 2)

Time to onset and death outcome statistics

More than 70% of coagulopathy events associated with echinocandins were concentrated in the first 10 days of drug initiation, and the proportion of onset times exceeding 40 days was higher than for polyenes and triazoles. The top four shortest median onset time are: anidulafungin 0 (IQR 0-10.5), caspofungin 2.5 (IQR 0.25-7), micafungin 4 (IQR 1–9) and amphotericin B 4 (IQR 1–10). (Fig. 3)

The top four drugs in terms of mortality were: caspofungin (57.03%), amphotericin B (54.11%), micafungin (50.93%) and anidulafungin (50.00%). Isavuconazole has the lowest mortality rate (12.50%). (Fig. 4)

Discussion

Although our results showed that anidulafungin, caspofungin and micafungin had significantly higher signal strength than triazoles and polyenes in coagulation dysfunction. At present, we can only find a small amount of research on the mechanism of micafungin leading to

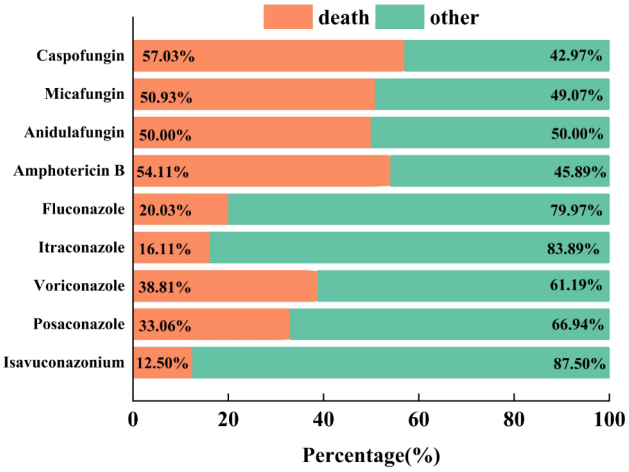

Fig. 4 The fatality rate related to coagulation dysfunction

coagulation dysfunction, and caspofungin and anidulafungin are almost none.

The results of a case report show that the occurrence of TTP is most likely related to the use of micafungin by a mechanism that may be due to the fact that micafungin alters the function of ADAMTS13 or reduces the activity of ADAMTS13 through other pathways, which results in the circulation of von Willebrand factor (vWF), which in turn leads to the development of a platelet aggregant. ADAMTS13 works by cleaving vWF preventing it from forming large molecules, thus avoiding platelet aggregation [12]. Another view is that micafungin promotes thrombosis by causing eryptosis, which is accompanied by cell shrinkage [13] and cell membrane scrambling with phosphatidylserine translocation to the cell surface [14]. This view was confirmed in an in vitro cell trial [15]. It is worth noting that our results also showed a very strong signal between micafungen and TTP (ROR 20.43, 95%CI: 8.49–49.14) (Fig. 2). The patient in this report suffered cardiac arrest the day after the onset of TTP and subsequently died [12]. TTP is often fatal and if left untreated, usually results in death in 10–15 days [12]. Therefore, when necessary, patients using micafunzin should be monitored for laboratory indicators related to thrombosis, especially in the intensive care unit, because they are less able to describe their health than patients with mild disease. Although no relevant studies on micafungin and DIC were found, since it is clinically difficult to completely differentiate TTP from DIC [16], coupled with the fact that our results showed a very strong signal strength between micafungin and DIC (ROR 27.19, 95%CI 18.49–39.98), we believe that there is still a need to measure the coagulation parameters when using micafungin especially in patients with poor health.

In a multicentre phase IV clinical study, the AEs with the highest incidence in the micafungin group was decreased platelet count (8.2%) [17]. Results from another phase III clinical trial showed a 10% incidence of thrombocytopenia in the micafungin treatment group [10]. Our results also showed that positive signals were demonstrated between micafungin and both platelet count decreased (ROR 3.50, 95%CI: 2.36–5.19) and thrombocytopenia (ROR 2.87, 95%CI: 1.87–4.41). However, the exact mechanism is unclear.

Another case report documented that micafungin caused a patient to develop pure red cell aplasia (PRCA), which returned to normal levels after discontinuing micafungin [18]. The mechanism of its occurrence may be related to the immune response and metabolic pathways, but the exact mechanism is not known [19]. In addition, it has been reported that micafungin may cause immune complex type hemolytic anemia [20]. The main causes of drug-induced haemolytic anaemia include immunological or oxidative destruction of red blood cells (RBC). Drug-induced hemolysis of immune type can be divided into drug-dependent antibody mediated or drug-independent antibody mediated. The immune complex type is one of the drug-dependent antibody mediated types [21]. The evidence suggests that after the patient was given micafunzin, the body produced antibodies that could bind to micafunzin, and this complex caused the development of hemolytic anemia [20]. Although this type of hemolysis is very rare, it can be fatal. Therefore, as soon as micafungin is suspected of causing haemolysis in a patient, the drug should be discontinued and targeted treatment should be administered. There is a high degree of suspicion that the hemolysis caused by micafungine is closely related to bleeding at different sites. Our results also seem to support this hypothesis. The ROR (95%CI) between micafungine and gastrointestinal haemorrhage, cerebral haemorrhage and pulmonary haemorrhage were respectively: 3.17 (2.02–4.97), 4.95 (2.81–8.72), 5.53 (1.78–17.16). The results showed the strongest association between pulmonary haemorrhage and micafungin, followed by cerebral haemorrhage and gastrointestinal haemorrhage. This observation may be attributed to the location of fungal infection in the patient and the lungs are frequently susceptible to fungal infections.

In contrast, data on caspofungin and anidulafungin in coagulation dysfunction are mainly clinical trials and a few case reports, and the sample sizes are small. Results of a safety study of caspofungin showed that thrombocytopenia occurred in <4% of patients in the caspofungin treatment group [22]. One study found the presence of platelet antibodies in a patient with caspofungin-induced thrombocytopenia by laboratory examination, and the normal bone marrow examination suggests that peripheral destruction of platelets may be the mechanism of caspofungin-induced thrombocytopenia rather than inhibition of platelet production [23]. The fact that there is an overlap between platelet count decreased and

thrombocytopenia also makes it difficult for spontaneous reporters to distinguish between the two. Another study showed that caspofungin prolonged prothrombin time, activated partial thromboplastin time (aPTT), and international normalized ratio (INR) in patients with moderate-to-severe hepatic dysfunction, where the mean time of aPTT was prolonged by up to 5 s [24]. A case report shows that a small-intestine transplant patient treated with caspofungin developed DIC and eventually died [25]. In the analysis of the risk factors for linezolid-induced thrombocytopenia, the use of caspofungin was shown to be an independent risk factor [26, 27]. Our results showed a strong signal between caspofungin and pulmonary haemorrhage (ROR 20.76, 95%CI 11.78–36.59), but we didn't find any relevant case reports, perhaps the positive signal may be related to the disease itself, just like invasive aspergillosis usually involves the lungs and can lead to bleeding in the lungs and gastrointestinal tract [28]. Nevertheless, the exact mechanism by which caspofungin causes coagulation dysfunction remains inconclusive.

Similarly, the results of a clinical trial of anidulafungin in children under 2 years showed a 10.5% incidence of thrombocytopenia, which was the only AE associated with the blood and lymphatic system. Our results similarly showed that anidulafungin showed stronger signal strength only with thrombocytopenia (ROR 9.75, 95%CI 5.22–18.19), and the two results and seem to be in agreement with each other. In another clinical trial in patients aged 2–18 years, the incidence of epistaxis in the micafungin group was 16.3%. The incidence of platelet count decreased decline was 10.20% and the incidence of DIC, cerebral haemorrhage, gastrointestinal haemorrhage and coagulopathy were all 2.04% [29]. More other post-marketing safety data were not found. Thus, we summarized the current potential mechanisms by which antimicrobials cause coagulation dysfunction: (1) Reducing synthesis of vitamin K-dependent coagulation factors II, VII, IX, and X by inhibiting vitamin K production of intestinal flora, e.g. cefoperazone [30, 31]. (2) Reducing fibrinogen by affecting liver function or gene expression, which causes coagulation dysfunction, such as tigecycline and fluconazole [32]. (3) Reducing platelet production by myelosuppression [33] or by immune-mediated increase in platelet clear [34]. (4) Drug interactions, such as fluconazole can lead to increased blood levels of superwarfarin and cause coagulation dysfunction [35]. These theories may be useful for further mechanistic studies.

An interesting topic is what is the risk of coagulation dysfunction in obese patients using echinocandins. More and more studies suggest that exposure to echinocandins is lower in obese patients compared to non-obese patients [36]. However, it has also been suggested that obese patients have a faster coagulation rate and greater antifibrinolytic capacity compared to the healthy population [37, 38]. These two conclusions may seem contradictory, and there are no studies on the risk of coagulation dysfunction in obese patients using echinocandins. This is worth exploring in depth.

In addition, considering that more than 70% AEs related with coagulation dysfunction in echinocandins occur in the first 10 days, coagulation parameters should be monitored regularly during the first week of drug use. Whether there is a causal relationship between high mortality and echinocandins needs to be explored in more rigorous studies, but it is certain that patients need to be alerted to a sudden deterioration in their health status during the use of echinocandins and amphotericin B. This is because once a coagulopathic event occurs, the patient is likely to die.

Although the study systematically predicted the risk of echinocandins and other antifungal drugs on coagulation dysfunction, there are still shortcomings. Firstly, the study does not prove a causal relationship between echinocandins and coagulation dysfunction, and the findings are only a speculation based on an algorithm. Second, the data included in the study may not fully reflect the real situation, as there are some errors or missing data in the self-reported reports. Third, the study was unable to determine the incidence of coagulation dysfunction because the total number of reports of the target patients as well as the target AEs were unknown. Lastly, the study could not rule out bias from the disease itself and drug interactions.

Conclusions

Our findings predict a higher association between echinocandins and coagulation disorders than both triazoles and polyenes. Moreover, of the three echinocandins, anidulafungin had the strongest association with coagulation dysfunction, followed by micafungin and caspofungin. The exact causality needs to be verified by further randomized controlled trials.

Abbreviations

FAERS	Food and drug administration adverse event reporting system
ROR	Reporting odds ratio
PS	Primary suspect
IQR	Interquartile range
DIC	Disseminated intravascular coagulation
TTP	Thrombotic thrombocytopenic purpura
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
PT	Preferred term
MedDRA	Medical dictionary for regulatory activity
vWF	Von willebrand factor
PRCA	Pure red cell aplasia
RBC	Red blood cell
aPTT	Activated partial thromboplastin time
INR	International normalized ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12959-024-00641-4.

Supplementary Material 1: Preferred terms related to coagulation dysfunction in MeDRA

Supplementary Material 2: Clinical characteristics of patients with caspofungin associated coagulation dysfunction events

Supplementary Material 3: Clinical characteristics of patients with micafungin-associated coagulation dysfunction events.

Supplementary Material 4: The calculation formula of disproportionality analysis and the criterion of positive

Supplementary Material 5: Target drugs and corresponding search terms

Supplementary Material 6: Clinical characteristics of patients with anidulafungin -associated coagulation dysfunction events.

Supplementary Material 7: Overall coagulation dysfunction signals and RORs comparing different drugs with the full database (Excluding consumer reports)

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Author contributions
Conception or design of the work: QC, and YW. Acquisition, analysis or interpretation of data: QC. Drafting the article: YW. Software: Zy Y. All authors critically reviewed the manuscript and participated in the interpretation of the results. The final manuscript was read, checked and approved by all authors.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
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