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ORIGINAL RESEARCH

Real-World Efficacy and Safety of Liposomal Amphotericin B for Invasive Fungal Disease in Patients with Hematologic Malignancies: A Multicenter Retrospective Study

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Purpose: Patients with hematologic malignancies are highly vulnerable to invasive fungal disease (IFD). Despite the broad-spectrum efficacy and lower toxicity of liposomal amphotericin B (L-AmB), there is a lack of real-world evidence on the recently approved domestic L-AmB in China. This study aims to evaluate its real-world efficacy and safety in patients with hematologic malignancies.

Patients and Methods: This study retrospectively and consecutively included hematologic malignancies patients with IFD who received domestic L-AmB treatment in China between December 2024 and May 2025. Efficacy was evaluated by overall treatment success, and safety assessment was based on adverse events (AEs). A composite outcome of treatment success without severe AEs (≥ Grade 3) was used to evaluate the clinical benefit-risk balance.

Results: A total of 100 eligible patients were included in this analysis, with a median duration of L-AmB treatment of 12 days (interquartile range [IQR], 7–19 days). The overall treatment success rate was 71.0% (71/100). Subgroup analysis demonstrated that longer treatment duration, acute lymphoblastic leukemia (ALL), and undefined or possible IFD categories were associated with a numerically higher treatment success rate. Furthermore, L-AmB exhibited a favorable safety profile, with mostly mild-to-moderate AEs. Hypokalemia was the most frequent (52.0%) but manageable, whereas nephrotoxicity, hepatotoxicity, and infusion-related reactions were mild. Notably, a total of 51 patients (51%) achieved treatment success without severe AEs, demonstrating an overall favorable benefit-risk balance. Dose-duration stratified composite outcome analysis showed that the longer treatment duration group (> 14 days) generally exhibited a superior benefit-risk balance (range 63.6%-84.6%).

Conclusion: Our findings support L-AmB as a clinically effective and well-tolerated therapeutic option for patients with hematologic malignancies complicated by IFD.

Keywords: efficacy, hematologic malignancy, invasive fungal disease, liposomal amphotericin B, safety

Introduction

Patients with hematologic malignancies have a high risk of invasive fungal diseases (IFDs) owing to prolonged neutropenia and immune dysfunction induced by intensive therapies.[1] Reported data from China show that the incidence rates of probable and proven IFD are 2.1% in patients with hematological malignancies undergoing chemotherapy and 7.7% in recipients of hematopoietic stem cell transplantation (HSCT).[2] Additionally, IFDs have been documented as one of the complications following chimeric antigen receptor-T cell immunotherapy, representing a major challenge in the management of patients with hematologic malignancies.[3] Despite advances in antifungal prophylaxis and treatment, IFDs (eg., aspergillosis, candidiasis, mucormycosis) remain leading cause of morbidity and mortality in this population, with

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case fatality rates ranging from 30% to 70%.[4,5] The widespread prophylactic use of triazole antifungals for IFD has been associated with an increasing incidence of multidrug-resistant and rare fungal infections in recent years, highlighting the urgent clinical need for rapidly acting, broad-spectrum antifungal agents.[6]

Amphotericin B, with its rapid and broad-spectrum fungicidal properties, remains an indispensable cornerstone drug in scenarios demanding broad empiric coverage, suspected resistance, or requiring rapid pathogen eradication.[7,8] However, its conventional formulations, such as deoxycholate and lipid complexes, are restricted in clinical application due to infusion reactions and dose-limiting nephrotoxicity.[9,10] Notably, liposomal amphotericin B (L-AmB) overcomes these limitations by encapsulating amphotericin B within a monolayer liposome, thereby reshaping its distribution in tissue.[11] This formulation substantially reduced nephrotoxicity and infusion reactions while preserving its broad and rapid fungicidal activity.[11–13] High-level evidence from randomized controlled trials supported this advantage: a multicenter study confirmed L-AmB's superior efficacy and safety compared to traditional deoxycholate formulations in treating neutropenia-associated IFD.[14] Additionally, a study demonstrated that high-dose L-AmB can completely cure chronic disseminated candidiasis in hematologic patients.[15] Accordingly, L-AmB has emerged as a key treatment for this spectrum of life-threatening infections.

Although the efficacy of L-AmB is widely recognized, clinical outcomes may not be interchangeable across different L-AmB formulations. As the originator L-AmB, AmBisome® has been widely adopted in clinical practice; however, its reliance on imports results in substantial cost barriers and restricted availability. Ansulike® (CSPC Ouyi Pharmaceutical Co., Ltd., Shijiazhuang, China) is a recently approved domestic L-AmB formulation in China, which obtained regulatory approval on September 10, 2024, following completion of consistency evaluation. It is equivalent to the originator L-AmB in liposomal composition, active ingredient, and excipients, with similar pharmacokinetic characteristics, antifungal activity, and safety profile. Meanwhile, it offers reduced treatment costs and enhanced clinical accessibility for Chinese patients. However, real-world evidence regarding the efficacy and safety of domestic L-AmB remains limited, particularly in the high-risk population of patients with hematological malignancies. Therefore, we conducted a multicenter retrospective study to first evaluate the real-world clinical outcomes of domestic L-AmB in patients with hematologic malignancies complicated by IFD.

Materials and Methods

Study Design

This exploratory retrospective study analyzed real-world clinical data from patients with hematologic malignancies complicated by IFD who received domestic L-AmB treatment at three tertiary referral hospitals in China between December 2024 and May 2025. The three tertiary referral hospitals are all specialized centers for the diagnosis and treatment of hematological malignancies and HSCT. The diagnostic, treatment, efficacy, and safety assessment procedures are consistent across the centers, all adhering to the Chinese 6th-revision IFD diagnosis and treatment guidelines.[2] This short study period immediately following approval was designed to obtain earliest real-world data, reduce temporal biases in practice or prophylaxis, and to capture short-term outcomes in IFD, a critical disease. The study flowchart is shown in Figure 1. This study was carried out in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Initial approval was granted by the Ethics Committee of the Soochow Hopes Hematonosis Hospital (Approval No.2025–017), with subsequent approval obtained from all participating sites. Due to the retrospective nature of this investigation, written informed consent was waived and approved by our ethics committee.

Study Population

This study consecutively included hematologic malignancies patients with IFD who received domestic L-AmB treatment. Inclusion criteria were: (i) age unrestricted, either sex; (ii) confirmed hematologic malignancy, including acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndromes (MDS), lymphoma, multiple myeloma (MM) and aplastic anemia (AA) were clinically and pathologically diagnosed; (iii) Confirmed or suspected IFD and administration of domestic L-AmB for ≥3 days. The exclusion criteria were: (1) patients with incomplete

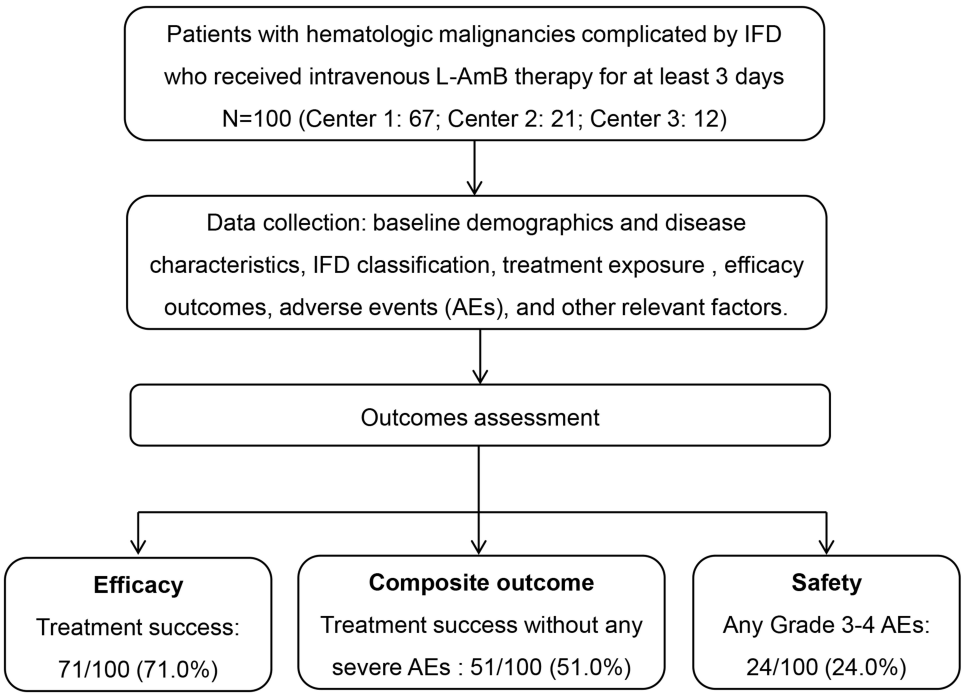

Figure 1 The flow chart of the study.
Abbreviations: AEs, adverse events; IFD, invasive fungal disease; L-AmB, Liposomal amphotericin B.

medical records or other factors that could affect the assessment of efficacy and safety; (2) patients deemed unsuitable for participation in this study by the clinicians. In accordance with the Chinese 6th-revision IFD classification criteria,[2] IFD was categorized into febrile neutropenia (FN), undefined IFD, possible IFD, probable IFD, and proven IFD (Table S1). The definitions of possible/probable/proven IFD were consistent with the EORTC/MSG criteria.[16] In contrast, according to the Chinese 6th-revision guidelines, FN was defined as the presence of fever (single oral temperature ≥ 38.3°C or a temperature of ≥ 38.0°C lasting for more than 1 hour) in the setting of neutropenia (absolute neutrophil count < 0.5×10^9/L, or < 1.0×10^9/L with an expected decline to < 0.5×10^9/L within 48 hours). Undefined IFD was defined as the presence of at least one host factor plus clinical imaging abnormalities or positive serum galactomannan (GM)/glucan (G) tests in patients.

Treatments and Procedures

All patients received L-AmB at a dose of 3 mg/kg per day, with dose adjustments and adjunctive therapies administered by clinicians based on individual patient conditions. Antifungal treatment strictly adhered to the principles of the Chinese 6th-revision IFD diagnosis and treatment guidelines.[2] Patients with FN, undefined, and possible IFD received empirical/diagnostic-driven therapy, and probable IFD patients received targeted therapy. Dose adjustments were primarily applied to elderly patients (aged ≥ 60 years) and those who developed renal impairment during treatment. To ensure safety, the dosage was promptly reduced upon detection of a ≥ 25% increase in serum creatinine from baseline or when clinically significant renal dysfunction occurred. Concomitant antifungal therapy was permitted during L-AmB administration as determined by the clinicians, and the use, type, dosage, duration, and any oral step-down strategies combination therapy were systematically recorded using a standardized case report form.

Treatment-related data were systematically extracted from the medical records using a standardized electronic case report form. Data capture covered the period from 7 days before treatment initiation, throughout the entire treatment course, and up to 7 days after treatment completion. Collected data included: baseline demographics and disease characteristics (age, sex, hematologic malignancy, laboratory tests, imaging, and prior antifungal prophylaxis or therapy), infection characteristics (infection site and pathogenic type), IFD classification, treatment exposure (initial dose, daily

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dose, cumulative dose, treatment duration, premedication, and combination antifungal drugs), efficacy outcomes, adverse events (AEs), and other relevant factors.

Outcome Assessment

Efficacy assessment was conducted using all clinical, imaging, and microbiological information recorded during therapy and within 7 days after discontinuation. The primary outcome was overall treatment success assessed at the end of L-AmB therapy or within 7 days after treatment completion. Treatment success was defined in accordance with the Mycoses Study Group and European Organization for Research and Treatment of Cancer (MSG-EORTC) Consensus Criteria as complete or partial remission of IFD-related clinical signs/symptoms, combined with imaging improvement on follow-up and/or microbiological clearance (if baseline mycological evidence was present and repeats testing was performed).[17] Clinical symptoms and radiological findings of IFD in patients with hematological malignancies typically improve or reach an early clinical response within 7 days after treatment completion. Therefore, this study focused on the short-term clinical outcomes of L-AmB for IFD, which aligns with the core therapeutic goal of rapid infection control in critically ill hematologic malignancies patients.[2,18]

Given that the majority of patients with hematologic malignancies receive subsequent intensive therapies (eg., chemotherapy or hematopoietic stem cell transplantation) shortly after completing L-AmB treatment, adverse events (AEs) occurring beyond 7 days post-treatment may not be reliably attributed to L-AmB.[17] Therefore, the safety of L-AmB was evaluated by assessing the incidence of AEs during the treatment period and within 7 days after treatment completion. AEs of interest included nephrotoxicity, hepatotoxicity, hypokalemia, and infusion-related reactions. All AEs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE version 5.0). Moreover, secondary outcome was the benefit-risk composite defined as treatment success without any severe AEs (≥ Grade 3), which was used to summarize the net clinical benefit with a clinically meaningful toxicity threshold.

Statistical Analysis

Data analyses were performed using R version 4.2.2 and Stata version 17.0. Continuous variables were summarized as the mean ± standard deviation (SD) or the median (interquartile range [IQR]); categorical variables were presented as frequencies and percentages (%). Chi-square (χ^2) tests or Fisher's exact test were used to compare categorical variables between groups. To minimize potential biases, we adopted a multicenter design to enhance generalizability, used standardized electronic case report forms for data collection, strictly followed predefined criteria for patient selection, and based all assessments on routine clinical records and standardized criteria. Furthermore, subgroup analyses of treatment success by L-AmB treatment duration, underlying hematologic malignancy type, and baseline IFD classification were also conducted. Moreover, logistic regression was employed to adjust for potential confounders and identify factors associated with treatment success and severe AEs. Variables for multivariate analysis were prespecified based on clinical relevance and published evidence.[19] For the treatment success, the variables examined include treatment duration, daily dose, combination antifungal therapy, and neutropenia grade. For severe AEs, univariate and multivariate analyses were conducted on the cumulative dose and combination antifungal therapy. The benefit-risk composite was evaluated across strata of daily dose (<2, 2–3, >3 mg/kg/day) and duration (<7, 7–13, ≥14 days), with descriptive results presented as n/N (%). Missing data were rare and handled by complete-case analysis. All patients had complete follow-up data without clinically relevant loss to follow-up. All statistical tests were two-sided and a p-value <0.05 was considered statistically significant.

Results

Baseline Characteristics

A total of 100 patients were included in this study, with a median age of 51 years (IQR, 31–64) and a male predominance (68.0%). The underlying hematologic malignancies were primarily AML (49.0%), followed by MDS (17.0%) and ALL (15.0%). Among the 100 patients included in this study, 45 (45.0%) had undergone HSCT. At treatment initiation, the baseline IFD status was classified as undefined IFD in 52.0% of patients, possible IFD in 26.0%, probable IFD in 14.0%,

and FN in 8.0%. Lung (89.0%) was the most common site of infection. Among patients with identified pathogens, *Aspergillus* species were the most common (26/33, 78.8%). In total, 83% of patients had received prior antifungal therapy, with posaconazole (39/83, 47.0%), caspofungin (34/83, 41.0%), and voriconazole (23/74, 27.7%) being the most frequently used. Detailed patient characteristics are presented in Table 1.

L-AmB Treatment

As shown in Table 2, the proportions of patients receiving empirical therapy, diagnostic-driven therapy, and targeted therapy were 8%, 78%, and 14%, respectively. Prior to L-AmB infusion, 15.0% of patients received premedication to prevent or reduce infusion-related reactions. Of these, 13 patients (86.7%) received dexamethasone and 2 patients (13.3%) received promethazine. Regarding L-AmB administration, the median duration was 12 days (IQR, 7–19 days), with a mean daily dose of 2.43 ± 0.80 mg/kg and a mean cumulative dose of 1,884.5 ± 1,565.8 mg. During the

Table 1 The Demographic and Clinical Characteristics of Patients

Characteristics	Overall (n = 100)
Age (years), median (IQR)	51 (31, 64)
Gender, n (%)	
Male	68 (68.0)
Female	32 (32.0)
Underlying hematologic malignancies, n (%)	
Acute myeloid leukemia	49 (49.0)
Acute lymphoblastic leukemia	15 (15.0)
Myelodysplastic syndrome	17 (17.0)
Lymphoma	5 (5.0)
Multiple myeloma	1 (1.0)
Others	12 (12.0)
HSCT	45 (45.0)
Diagnosis, n (%)	
Febrile neutropenia	8 (8.0)
Undefined IFD	52 (52.0)
Possible IFD	26 (26.0)
Probable IFD	14 (14.0)
Infection site n (%)	
Lung	89 (89.0)
Others	11 (11.0)
Pathogen detected, n (%)	33 (33.0)
Aspergillus	26 (78.8)
Candida	7 (21.2)
Mucorales	3 (9.1)
Prior antifungal therapy, n (%)	83 (83.0)
Posaconazole	39 (47.0)
Caspofungin	34 (41.0)
Voriconazole	23 (27.7)
Main laboratory tests, median (IQR)	
Potassium (mmol/L)	3.9 (3.6, 4.3)
Creatinine (μmol/L)	56.0 (44.0, 69.3)
ALT (U/L)	20.0 (13.1, 37.9)
Neutrophils ($\times 10^9$/L)	1.4 (0.1, 3.3)

Abbreviations: ALT, alanine aminotransferase; HSCT, hematopoietic stem cell transplantation; IFD, invasive fungal disease.

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Table 2 The Administration of L-AmB of Patients

Characteristics	Overall (n = 100)
L-AmB therapy strategy, n (%)	
Empirical therapy	8 (8.0)
Diagnostic-driven therapy	78 (78.0)
Targeted therapy	14 (14.0)
Premedication n (%)	15 (15.0)
Dexamethasone	13 (86.7)
Promethazine	2 (13.3)
Administration dosages	
Treatment duration (days), median (IQR)	12 (7, 19)
Daily dose (mg/kg/day), mean ± SD	2.43 ± 0.80
Cumulative dose (mg), mean ± SD	1,884.48 ± 1,565.81
L-AmB therapy regimen, n (%)	
Monotherapy	26 (26.0)
Combination therapy	74 (74.0)
Posaconazole	25 (33.8)
Caspofungin	24 (32.4)
Isavuconazole	15 (20.3)
AmB-D (nebulization)	13 (17.6)
Voriconazole	10 (13.5)
Others*	3 (4.1)

Abbreviations: AmB-D, Amphotericin B deoxycholate; IQR, interquartile range; L-AmB, liposomal amphotericin B; SD, standard deviation. *Others included 1 case of micafungin and 2 cases of amphotericin B colloidal dispersion (nebulization).

treatment course, 74.0% of patients (74/100) received L-AmB in combination with other antifungal agents during the treatment course, primarily posaconazole (25/74, 33.8%), caspofungin (24/74, 32.4%), and isavuconazole (15/74, 20.3%).

Efficacy

A total of 71 patients achieved treatment success, corresponding to an overall success rate of 71.0% (71/100; 95% CI: 61.1–79.6). Subgroup analyses revealed numerically higher success rates with extended treatment durations (≥ 7 days: 73.8% vs. <7 days: 56.3%; ≥ 14 days: 78.3% vs. <14 days: 64.8%), though these differences did not achieve statistical significance (Figure 2 and Table 3). Notably, the ≥ 14-day subgroup demonstrated a 13.5 percentage point absolute increase in success rates compared to shorter durations. Stratification by underlying hematologic malignancies showed variable success rates, ranging from 40.0% in lymphoma to 86.7% in ALL, with AML and MDS demonstrating intermediate efficacy (73.5% and 64.7%, respectively), although between-group differences did not reach statistical significance. Regarding IFD classification, numerically higher success rates were observed for undefined IFD (75.0%) and possible IFD (76.9%) than for FN (50.0%) and probable IFD (57.1%), albeit without statistically significant differences across categories.

Safety

Safety assessment demonstrated that L-AmB was well-tolerated in patients with hematologic malignancies, and most AEs were mild to moderate in severity. As shown in Table 4, the most common AE was hypokalemia, occurring in 52.0% of patients (31.0% Grade 1–2; 21.0% Grade 3–4), followed by cough (29.0%, all Grade 1–2) and fever (20.0%; 17.0% Grade 1–2, 3.0% Grade 3–4). With respect to nephrotoxicity, elevated serum creatinine occurred in 13% of patients, and only one patient developed a Grade 3 event. As for hepatotoxicity, elevated alanine aminotransferase (ALT), aspartate

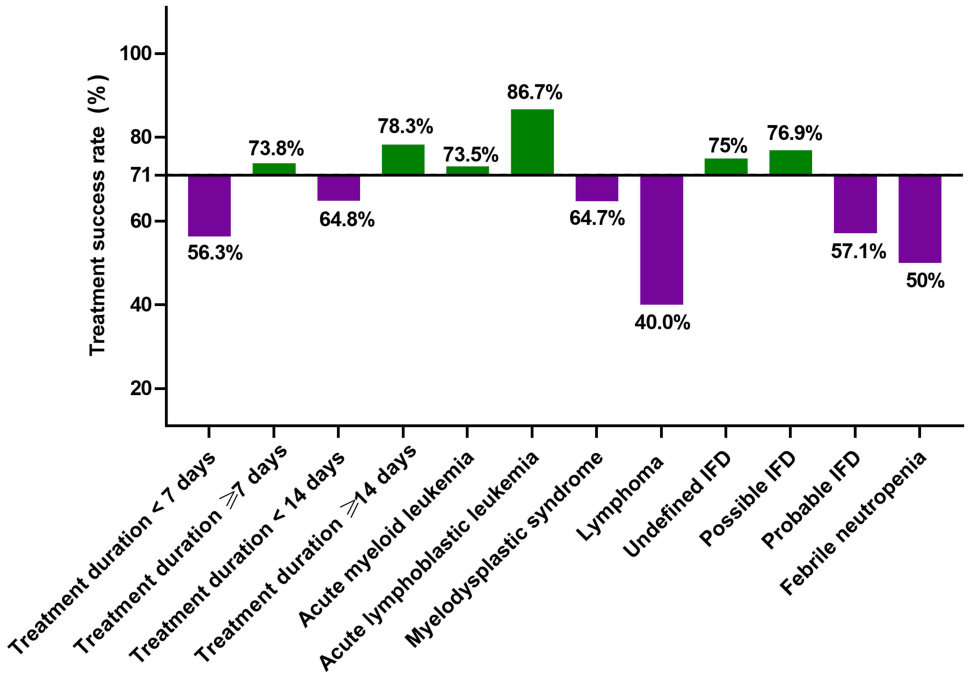

Figure 2 Treatment success rates in different subgroups.Green bars indicate a higher treatment success rate than the overall population, while purple bars indicate a lower one.
Abbreviations: IFD, invasive fungal disease.

transaminase (AST), and bilirubin were observed in (17.0%; 16.0% grade 1–2, 1.0% grade 3–4), (11.0%; 10.0% grade 1–2, 1.0% grade 3–4), and (13.0%; 12.0% grade 1–2, 1.0% grade 3–4) of patients, respectively. Infusion-related reactions included fever in 20% of patients (≥ Grade 3: 3%) and chills in 6% of patients.

Table 3 Efficacy Outcomes of L-AmB Therapy

	Treatment Success, n (%), [95% CI]	**p-value**
Overall treatment success (N = 100)	71 (71.0), [61.1–79.6]	—
Subgroup		
Treatment duration stratification		
Stratified by 7 days cutoff		0.16
< 7 days (n = 16)	9 (56.3), [29.9–80.2]	
≥ 7 days (n = 84)	62 (73.8), [63.1–82.8]	
Stratified by 14-day cutoff		
< 14 days (n = 54)	35 (64.8), [50.6–77.3]	0.14
≥ 14 days of therapy (n = 46)	36 (78.3), [63.6–89.1]	
Hematologic malignancy		0.58
Acute myeloid leukemia (n = 49)	36 (73.5) [58.7–84.7]	
Acute lymphoblastic leukemia (n = 15)	13 (86.7) [61.1–96.6]	
Myelodysplastic syndrome (n = 17)	11 (64.7) [41.3–82.8]	
Lymphoma (n = 5)	2 (40.0) [5.3–85.3]	
IFD Classification		0.28
Undefined IFD (n = 52)	39 (75.0) [61.8–84.8]	
Possible IFD (n = 26)	20 (76.9) [57.9–89.0]	
Probable IFD (n = 14)	8 (57.1) [32.6–78.6]	
Febrile neutropenia (n = 8)	4 (50.0) [21.5–78.5]	

Abbreviations: CI, confidence interval; IFD, invasive fungal disease.

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Table 4 Adverse Events Graded by CTCAE v5.0

Adverse Event, n (%)	Grade 1-2	Grade 3-4	Total (N = 100)
Composite across AEs*	60 (60.0)	24 (24.0)	84 (84.0)
Fever (≥1°C rise)	17 (17.0)	3 (3.0)	20 (20.0)
Chills	6 (6.0)	0	6 (6.0)
Nausea	10 (10.0)	0	10 (10.0)
Vomiting	7 (7.0)	0	7 (7.0)
Diarrhea	4 (4.0)	2 (2.0)	6 (6.0)
Cough	29 (29.0)	0	29 (29.0)
Hypokalemia	31 (31.0)	21 (21.0)	52 (52.0)
Elevated ALT	16 (16.0)	1 (1.0)	17 (17.0)
Elevated AST	10 (10.0)	1 (1.0)	11 (11.0)
Creatinine elevation	12 (12.0)	1 (1.0)	13 (13.0)
Elevated bilirubin	12 (12.0)	1 (1.0)	13 (13.0)
Hypocalcemia	17 (17.0)	0	17 (17.0)
Hyponatremia	5 (5.0)	0	5 (5.0)
Hypomagnesemia	11 (11.0)	0	11 (11.0)

Note: Grading per CTCAE v5.0.; Event rows are per-event; a patient may appear in multiple rows. Fever defined as ≥1°C above baseline during treatment. *Composite is per-patient (worst grade across AE); composite percentages do not equal sums of event rows.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase.

Table 5 Univariable and Multivariable Logistic Regression Analysis for Predictors of Treatment Success and Severe AEs

Predictor	Category	Univariable OR (95% CI)	p-value	Multivariable OR (95% CI)	p-value
Treatment success					
Duration	Per day	1.0 (1.0–1.1)	0.219	1.0 (1.0–1.1)	0.458
	≥14 days (Ref: <14 days)	1.8 (0.8–4.5)	0.182	-†	-
Daily dose	Per mg/kg/day	0.8 (0.4–1.4)	0.411	0.8 (0.4–1.4)	0.390
	>3 mg/kg/day (Ref: ≤3 mg/kg/day)	0.5 (0.2–1.6)	0.246	-†	-
Combination antifungal	Yes (Ref: No)	0.7 (0.2–2.3)	0.549	0.9 (0.2–3. 6)	0.932
Neutropenia grade	Per grade (0–4)	0.9 (0.7–1.1)	0.347	0.9 (0.6–1.1)	0.271
Severe adverse events					
Cumulative dose	>2500 mg (Ref: <2500 mg)	1.2 (0.4–3.2)	0.763	1.2 (0.4–3.4)	0.794
Combination antifungal	Yes (Ref: No)	2.7 (0.3–22.9)	0.352	2.8 (0.3–23.6)	0.343

Abbreviations: CI, confidence interval; OR, odds ratio; Ref, reference group. †Not included in the multivariable (adjusted) model to avoid collinearity with the continuous variable from the same domain.

Factors Associated with Treatment Success and Severe AEs

Univariate regression analysis for treatment success showed that several variables exhibited clinically observable trends toward improved outcomes, although no predictor reached statistical significance (all $p > 0.18$; Table 5). Specifically, treatment duration ≥ 14 days showed a favorable but non-significant association with treatment success (OR = 1.85, 95% CI 0.75–4.54; $p = 0.182$), corroborating the numerical trend observed in subgroup analyses (≥14 days of therapy: 78.3% vs. <14 days of therapy: 64.8%). In the multivariable model adjusted for duration (per day), daily dose (per mg/kg/day), combination antifungal therapy, and neutropenia grade, no factor was independently associated with treatment success (all $p > 0.25$). Furthermore, logistic regression analysis revealed that cumulative dose was not predictive of severe AEs (OR = 1.2, 95% CI 0.4–3.4, $p = 0.794$), while combination antifungal therapy was associated with a 2.8-fold higher odds of severe AEs, although this did not reach statistical significance (95% CI 0.3–23.6, $p = 0.343$).

Table 6 Comprehensive Efficacy-Safety Outcomes by Dose/Duration Category

Dose (mg/kg/day)	<7 days	7-13 days	≥14 days
<2	1/3 (33.3)	5/9 (55.6)	13/17 (76.5)
2-3	4/10 (40.0)	9/23 (39.1)	8/17 (47.1)
>3	1/3 (33.3)	3/6 (50.0)	7/12 (58.3)

Note: Values were presented as n/N (%), where n = number of patients achieving the composite outcome, and N = total number of patients in the corresponding category.

Benefit-Risk Balance

The benefit-risk balance analysis showed that 51 patients (51%) achieved the composite outcomes of treatment success without severe AEs, integrating efficacy and safety. When stratified by dose and duration (Table 6), the lowest composite rates were observed with short duration (<7 days) across all dosing groups (33–40%). With longer duration, the benefit-risk balance estimates showed an improving trend. However, this varied across dose subgroups, with the highest success rate observed in patients receiving <2 mg/kg/day for ≥14 days was 76.5% (13/17), followed by >3 mg/kg/day for >14 days (58.3%, 7/12) and 2–3 mg/kg/day for >14 days (47.1%, 8/17). Furthermore, among patients who developed grade 3–4 AEs, 20/24 (83.3%) still achieved treatment success, indicating that grade 3–4 AEs were manageable without compromising efficacy.

Discussion

As a crucial drug in antifungal treatment, L-AmB possesses distinct merits in terms of both efficacy and safety profile, thereby achieving a favorable balance between clinical benefits and drug toxicity. Our multicenter real-world analysis showed that among this high-risk population of patients with hematologic malignancies, L-AmB achieved an overall treatment success rate of 71%, with the majority of AEs being mild to moderate in severity. Notably, more than half of our patients (51%) attained treatment success without any grade 3–4 AEs, demonstrating potent antifungal efficacy and an acceptable safety profile for L-AmB in immunocompromised patients.

The overall treatment success rate of L-AmB in this study was 71.0%, consistent with previous efficacy data (60–70%) for L-AmB in patients with hematologic malignancies, further validating its stable efficacy in antifungal therapy.[20,21] In the setting of empirical antifungal therapy, a multicenter clinical study demonstrated that L-AmB achieved a response rate of 69% in patients with refractory FN. Concurrently, existing evidence indicated L-AmB remained effective in more challenging infection scenarios. For instance, Wu et al reported that L-AmB still yielded a treatment success rate of 77.5% among IFD patients who had failed prior antifungal therapy.[22] Consistently, 83% of our patients had received prior antifungals, yet our treatment success rate was comparable with previous studies. In contrast, a large-scale prospective study from Japan reported an overall response rate of 46.6% in a broader mixed population (FN/suspected fungal infection).[23] This discrepancy may reflect differences in patient eligibility criteria and endpoint definitions, highlighting the need to consider heterogeneity in patient populations when interpreting efficacy data.

Subgroup analysis revealed that longer L-AmB duration (≥7 days, particularly ≥14 days) were associated with numerically higher treatment success rates. This finding aligns with the pharmacokinetic characteristics of L-AmB, which requires continuous administration for 4–7 days to achieve steady-state concentrations.[24,25] Consequently, shorter treatment durations (eg., <7 days) may yield inadequate tissue drug exposure, compromising efficacy against deep-seated infections. Consistently, the favorable association between treatment duration ≥ 14 days and treatment success observed in regression analysis of our study highlights the importance of adequate treatment duration. Furthermore, stratified analysis by hematologic malignancy type showed numerically higher treatment success in ALL (86.7%) versus AML (73.5%) and MDS (64.7%), possibly reflecting more severe immunosuppression in AML/MDS patients that compromises fungal infection control.[26] Additionally, clinical practice advocates prompt empirical antifungal therapy in persistent FN, as earlier intervention correlates with better outcomes.[27,28] In our study, patients with undefined IFD and possible IFD demonstrated numerically higher success rates compared with those with probable IFD, highlighting

the importance of initiating treatment as early as possible before disease progression. However, the lower success rate observed in patients with FN may be attributable to the small sample size of this subgroup and resulting limited statistical power. Nonetheless, our findings overall align with the established recommendation that early amphotericin B-based therapy should be initiated when IFD is suspected.[22,29] Clinically, these findings provide a basis for L-AmB utilization in high-risk patients with hematologic malignancies, supporting early empirical initiation before disease progression and an adequately extended course to consolidate therapeutic efficacy.

Nephrotoxicity and electrolyte disturbances (especially hypokalemia) are well-documented risks of L-AmB.[30,31] Japanese nationwide data reported acute kidney injury in 30%-40% of patients, correlating with dose and baseline potassium levels.[32] Consistent with the known safety profile of lipid formulations, the present cohort demonstrated a 13% incidence of serum creatinine elevation (only 1% grade ≥3), reinforcing the favorable tolerability of L-AmB. Furthermore, although hypokalemia occurred in 52.0% of patients, it was generally manageable, suggesting that the safety profile of L-AmB can be improved through lower mean daily doses (2.4 mg/kg/day), enhanced monitoring, and prudent administration. Notably, hepatotoxicity was also minimal, with Grade 3–4 ALT, AST, and bilirubin elevations observed in just 1.0% each. Infusion-related reactions were uncommon despite premedication in only 15.0% of patients, indicating favorable infusion tolerability. Moreover, our regression analysis revealed a modest, nonsignificant increase in severe AEs with combination antifungal therapy, likely reflecting additive toxicities from overlapping adverse effect profiles. Collectively, these findings demonstrate an acceptable safety profile for L-AmB in this high-risk population, with toxicity patterns consistent with prior lipid formulation studies and manageable through dose optimization and vigilant monitoring.

Our findings suggest several potential implications for clinical practice. First, early initiation of L-AmB appeared to be associated with higher success rates, indicating that delays in initiation therapy may compromise outcomes and that expedited initiation could be beneficial. Second, 51% of patients achieved treatment success without severe AEs. In the composite outcome analysis stratified by dose-duration, treatment durations of at least 14 days appeared to enhance efficacy without a notable increase in severe AEs, suggesting that a two-week course may strike an appropriate balance between efficacy and safety. Furthermore, integrating refined antifungal management principles into clinical practice can further optimize the benefit-risk profile of L-AmB via rational patient selection, timely treatment initiation, optimized treatment duration and rigorous safety monitoring, which is of great importance for enhancing the clinical application value of L-AmB.[33]

While our study advances understanding, several limitations deserve mention. First, although the observed 71% treatment success rate aligned with efficacy rates previously reported outcomes in L-AmB studies, the retrospective and exploratory nature of this study introduces some bias. For instance, the patient population was heterogeneous, comprising both adults and children, as well as patients treated in general wards and intensive care units. However, due to the limited sample size, stratified analyses based on these factors could not be performed. Meanwhile, the small sample sizes in certain subgroups constrained the statistical power of subgroup analyses. Second, the timing of outcome assessment was not fixed on a specific day, which may introduce bias. Although subgroup analysis and multivariate regression did not find a significant impact of treatment duration on efficacy, this bias may still not be completely eliminated. Third, due to the lack of 30-day, 90-day, and IFD-related mortality data, a comprehensive assessment of its impact on survival outcomes could not be performed. Future studies should employ large-scale prospective cohorts or randomized controlled trials with fixed assessment time points (eg., day 30, day 90) and collect long-term outcomes, including IFD-related mortality.

Conclusions

In this real-world study of patients with hematologic malignancies complicated by suspected or probable IFD, L-AmB demonstrated stable and significant therapeutic efficacy with overall manageable safety. This finding provides practical evidence for the clinical application of L-AmB in this patient population. Future studies should focus on large-scale prospective clinical trials or real-world studies to validate optimal dosing regimens, long-term clinical efficacy and safety in specific patient subgroups, with subsequent integration of these findings into antifungal stewardship frameworks to inform clinical decision-making.

Data Sharing Statement

De-identified individual participant data that support the finding of this study are available at any time after publication from the corresponding author (Xiao Ma, Email: pony73sz@hotmail.com; Jun Wang, Email: wangjunsz@hotmail.com) upon reasonable request and with appropriate approvals.

Ethics Approval and Informed Consent

This study was carried out in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Initial approval was granted by the Ethics Committee of the Soochow Hopes Hematonosis Hospital (Approval No.2025-017), with subsequent approval obtained from all participating sites. Despite the informed consent was waived by the ethics committee of the Ethics Committee of the Soochow Hopes Hematonosis Hospital, we confirmed that the data of the patients included in this study was anonymized or maintained with confidentiality.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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