Global Journal of Microbiology Vol. 7, No. 1, November 12, 2026

Global *Journal of Microbiology*
2026; 7(1): 38-56.
ISSN Online: 2766-9513; ISSN Print: 2766-9505
Website: http://naturescholars.com
Email: Glo_J_Mic@126.com
Publisher: Scholars Publishing, LLC

Research Article

Prospective Interception at the Low Fungal Burden Stage: A Comparative Study of Diagnostic-Driven versus Empiric Antifungal Strategies in Febrile Patients with Hematological Malignancies

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Received: June 30, 2026; Accepted: July 5, 2026; Published online: November 12, 2026.
Cite this paper: Shan Liu, Xiaoxuan Liu, Mingxin He, Danyu Wang, Mengdi Jin, Jianhong Xiao, Liqiong Liu, Zhi Guo. Prospective Interception at the Low Fungal Burden Stage: A Comparative Study of Diagnostic-Driven versus Empiric Antifungal Strategies in Febrile Patients with Hematological Malignancies. *Global Journal of Microbiology*, 2026;7(1):38-56. http://naturescholars.com/gjmic.070106. https://doi.org/10.46633/gjmic.070106.
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Abstract

Objective: Empiric therapy (ET) for invasive fungal disease (IFD) in hematological malignancies often causes overtreatment. Diagnostic-driven therapy (DDT) offers a precision paradigm, but real-world host dynamics at clinical decision thresholds remain unclear. This study compared the clinical efficacy, safety, and biological profiles of ET versus DDT. **Methods:** We retrospectively analyzed 72 patients with hematological malignancies receiving systemic antifungals (ET, n=31; DDT, n=41) between 2023 and 2025. Inflammatory markers and fungal cell wall antigens (G/GM assays) were evaluated at treatment initiation. Multivariable logistic regression identified independent risk factors for breakthrough IFD and drug toxicities. One-year overall survival (OS) was analyzed using Kaplan-Meier methods. **Results:** Baseline characteristics were well-balanced (P>0.05). At treatment initiation, the DDT group had higher inflammatory loads (median CRP: 26.50 vs. 8.19 mg/L, P=0.0046) and active fever (46.3% vs. 9.7%, P<0.001), whereas the ET group had higher G/GM positivity (45.8% vs. 20.5%, P=0.0335). Multivariable regression showed DDT did not increase risks for breakthrough IFD (OR=1.35, 95% CI: 0.33–5.42, P=0.6754), hepatotoxicity, or nephrotoxicity. Kaplan-Meier analysis demonstrated equivalent 1-year OS (P=0.50). Baseline CRP predicted 1-year mortality better than PCT (AUC: 0.670 vs. 0.593). **Conclusions:** The DDT strategy provides comparable 1-year survival to ET without increasing breakthrough IFD or toxicities. Baseline CRP serves as a valuable prognostic biomarker for 1-year mortality in this population.

Key word: Hematological malignancies; Diagnostic-driven therapy; Empiric antifungal therapy; Invasive fungal disease; C-reactive protein.

Introduction

Patients with hematological malignancies or those undergoing intensive therapeutic interventions represent an exceptionally vulnerable population prone to life-threatening opportunistic infections. Among these, invasive fungal disease (IFD) remains a primary cause of morbidity and mortality, particularly during the profound and prolonged neutropenia phase induced by induction chemotherapy (1). Historically, because fungal pathogens progress rapidly and often insidiously within immunocompromised hosts, clinical management has relied heavily on the empiric therapy (ET) strategy. Under this paradigm, systemic antifungal agents are immediately initiated whenever a patient presents with prolonged neutropenic fever that is refractory to broad-spectrum antibacterial therapy for 4 to 7 days, irrespective of definitive microbiological or radiological evidence. Although ET prioritizes intervention speed to halt catastrophic systemic fungal dissemination, it frequently incurs high clinical costs. These include widespread overtreatment, cumulative organ toxicities, a heavy financial burden, and vulnerability to technical false-positive diagnostic noise caused by frequent infusions of human serum albumin or the co-administration of semi-synthetic β-lactam antibiotics (2).

To address these diagnostic and therapeutic limitations, the widespread adoption of high-resolution computed tomography (HRCT) and innovations in highly sensitive, non-culture-based circulating fungal cell wall antigen assays (G/GM tests) have collectively catalyzed a paradigm shift toward the diagnostic-driven therapy (DDT) strategy, also known as pre-emptive therapy (3,4). This precision-guided approach advocates for strategic restraint in the blind addition of systemic antifungals during early febrile phases. Instead, it relies on the serial monitoring of circulating biomarkers and early chest radiological evolution to construct a multidimensional chain of objective evidence prior to treatment initiation. Although several randomized controlled trials have confirmed the non-inferiority of DDT compared with traditional ET regarding long-term overall survival, significant academic controversy persists in real-world clinical practice (5,6). A critical scientific gap is that the host's microscopic biological dynamics and systemic inflammatory landscape at the precise chronological threshold when clinicians make antifungal decisions remain inadequately deconstructed at a sufficiently granular level. Specifically, it remains unclear whether the strategic waiting inherent to DDT permits unsafe, catastrophic proliferation of fungal pathogens or successfully achieves a more prospective, precise biological interception within a subclinical window of low fungal burden (7).

This study aimed to systematically deconstruct and compare the real-world clinical efficacy, safety margins, and baseline biological profiles of ET and DDT strategies in a cohort of febrile patients with hematological malignancies or following intensive medical interventions. By performing refined qualitative and quantitative evaluations of circulating fungal biomarkers and deconstructing the host's systemic inflammatory cascade at the precise historical moment of antifungal initiation, this study seeks to elucidate the behavioral landscape of real-world clinical decision-making. Furthermore, it aims to provide a rigorous, self-consistent, high-quality body of evidence-based medical data to optimize antifungal stewardship and advance precision medicine in the management of hematological infections

1. Materials and Methods

1.1 Patient Selection and Study Design

This study retrospectively analyzed the clinical data of 121 patients with hematological malignancies who received systemic antifungal therapy in the Department of Hematology at

Shenzhen Nanshan People's Hospital between January 2023 and December 2025. To establish a highly homogenous and unbiased study population, 49 patients were systematically excluded based on pre-specified criteria: a history of definitive proven IFD (n=5), prophylactic antifungal therapy (n=32), baseline proven IFD (n=5), and baseline probable IFD (n=7). Ultimately, 72 patients were formally enrolled, comprising 31 patients in the ET group and 41 patients in the DDT group.

1.2 Therapeutic Regimens and Clinical Stratification Criteria

The clinical diagnosis and therapeutic regimens for all enrolled patients were strictly in accordance with the Diagnostic Criteria and Principles of Treatment for Invasive Fungal Infections in Patients with Hematological Diseases/Malignancies formulated by the Chinese Invasive Fungal Infection Working Group. Patient cohort assignment was entirely determined by the specific clinical, laboratory, or radiological thresholds that triggered the initiation of systemic antifungals. For the ET group, the starting point was defined as prolonged neutropenia (absolute neutrophil count [ANC] $<0.5\times10^9$/L) accompanied by refractory fever unresponsive to standardized broad-spectrum antibacterial therapy for 4 days. Fever was defined as a single oral temperature measurement ⩾38.3°C (corresponding to an axillary temperature⩾38.0°C), or an oral temperature⩾38.0°C (corresponding to an axillary temperature ⩾ 37.7°C) sustained for more than 1 hour. In contrast, the initiation of antifungal therapy in the DDT group did not depend on the duration of fever. This strategy used the acquisition of multidimensional objective evidence as the treatment threshold; intervention was initiated immediately upon the presentation of relevant clinical symptoms, radiological evolution, or microbiological evidence such as a positive G/GM test. Regarding specific drug selection and regimen application, patients in both groups received targeted systemic antifungal therapy with voriconazole, posaconazole, or caspofungin based on the attending physician's assessment, administered as either targeted monotherapy or intensified combination protocols (8).

1.3 Clinical and Laboratory Evaluations

Baseline demographics, primary hematological malignancy sub-classification, and detailed histories of prior immunosuppressive therapies—including chronic corticosteroid use and recent exposure to immunosuppressants—were comprehensively extracted from the electronic medical record system. Longitudinal laboratory parameters, including ANC, platelet count (PLT), and routine coagulation indices (particularly D-dimer and fibrinogen [FIB] concentrations), were systematically collected to establish baseline homogeneity between the treatment groups. At the precise chronological node of systemic antifungal initiation, peripheral blood samples were immediately collected to determine C-reactive protein (CRP) and procalcitonin (PCT) concentrations to quantitatively assess the host's systemic inflammatory burden. The maximum temperature (Tmax) recorded within the subsequent 24 hours was also documented. Concurrently, the expression dynamics of peripheral blood fungal biomarkers were evaluated using dual qualitative and quantitative biological methods; in the quantitative analysis, left-censored data falling below the lower limit of detection were uniformly assigned a standard baseline value of 10.00 for standardized statistical processing.

1.4 Outcome Measures and Safety Definitions

The primary efficacy endpoint was the incidence of IFD. The diagnostic grading of IFD was strictly categorized as "proven" or "probable" based on the latest revised consensus criteria of the European Organisation for Research and Treatment of Cancer/Mycoses Study Group Education and Research Consortium (EORTC/MSGERC). Safety and tolerability endpoints included a rigorous assessment of organ toxicities directly attributable to systemic antifungal agents. Hepatotoxicity was defined as a definitive elevation of serum

transaminases or total bilirubin levels to more than three times the upper limit of normal (ULN). Nephrotoxicity was defined as a doubling of serum creatinine from baseline or an absolute increase exceeding 0.3 mg/dL. Secondary clinical outcomes encompassed the median duration of systemic antifungal therapy, the total length of hospital stay calculated from the onset of the index febrile episode, and the 1-year overall survival rate established via a continuous 365-day follow-up period.

1.5 Statistical Analysis

Continuous variables were evaluated for normality using the Shapiro-Wilk test. Given their non-parametric distribution, statistical descriptions are expressed as medians with interquartile ranges (IQRs), and intergroup comparisons were performed using the Mann-Whitney U test. Categorical variables are presented as absolute frequencies and corresponding percentages, analyzed using the Pearson chi-square test, or Fisher's exact test if the expected cell counts were too low. To isolate the independent effects of the different therapeutic strategies on IFD and drug-induced toxicities, multivariable logistic regression models were constructed, fully adjusting for key potential baseline confounders including age, primary tumor subtype, history of chronic steroid therapy, and the duration of profound neutropenia. Cumulative 1-year overall survival curves were estimated using the Kaplan-Meier method, and the log-rank test was applied to assess long-term survival non-inferiority and equivalence across the follow-up period.

Table 1. Baseline Demographics and Clinical Characteristics of the Study Cohort

Characteristic	ET Group (n=31)	DDT Group (n=41)	*P*
Demographics & Age			
Sex, n (%)			0.712
M	18 (58.1%)	22 (53.7%)	
F	13 (41.9%)	19 (46.3%)	
Age (years), median (IQR)	52 (41–61)	50 (39–63)	0.654
≥65 years old, n (%)	5 (16.1%)	7 (17.1%)	0.912
Disease Characteristics			
Case Classification, n (%)			0.763
Type C	14 (45.2%)	20 (48.8%)	
Type D	17 (54.8%)	21 (51.2%)	
Primary Disease Type, n (%)			0.994
AL	15 (48.4%)	19 (46.3%)	
MM	3 (9.7%)	4 (9.8%)	
CML/CLL	2 (6.5%)	3 (7.3%)	
MDS	4 (12.9%)	5 (12.2%)	
Lymphoma	7 (22.6%)	10 (24.4%)	
Treatment Stage, n (%)			0.968
Untreated	2 (6.5%)	3 (7.3%)	
Induction chemotherapy	14 (45.2%)	18 (43.9%)	
R/R or 2nd-line	6 (19.4%)	9 (22.0%)	
Consolidation/Maintenance	9 (29.0%)	11 (26.8%)	

Note: Abbreviations: ET, Empiric Therapy; DDT, Diagnostic-Driven Therapy; ANC, Absolute Neutrophil Count; PLT, Platelet; CRP, C-reactive protein; PCT, Procalcitonin

Furthermore, the prognostic performance of baseline inflammatory biomarkers at the time of treatment initiation for predicting 1-year all-cause mortality was established by calculating the area under the receiver operating characteristic curve (AUC-ROC) and its 95% confidence interval (CI). All statistical tests were two-sided, and a P value<0.05 was considered statistically significant. All data computation, statistical modeling, and academic plotting were executed within the R (version 4.5.2) and RStudio compilation environments.

2. Results

2.1 Baseline Data and Laboratory Parameters

This retrospective study ultimately included 72 febrile patients with hematological malignancies or following medical interventions who received systemic antifungal therapy, comprising 31 in the ET group and 41 in the DDT group (Table 1). Further comparative analysis of baseline laboratory indicators and median peak temperatures was performed. Regarding hematopoietic function and routine coagulation profiles at the threshold of triggering systemic antifungal administration, the baseline ANC was 2.87*10^9/L in the ET group versus 2.16*10^9/L in the DDT group (P=0.4667); platelet counts were 85*10^9/L versus 97*10^9/L, respectively (P=0.9819). Additionally, D-dimer levels were 1.05 mg/L versus 0.91 mg/L (P=0.7499), and fibrinogen levels were 3.48 g/L versus 3.74 g/L (P=0.1759), with none of these indicators showing statistically significant differences in distribution between the two groups.

In contrast, indicators reflecting the patients' systemic inflammatory status and febrile characteristics demonstrated significant statistical differences between the two groups. Statistical data showed that C-reactive protein at the time of treatment trigger was 26.50 mg/L in the DDT group, significantly higher than the 8.19 mg/L in the ET group (P=0.0046). Similarly, procalcitonin was also higher in the DDT group than in the ET group (0.26 ng/mL vs. 0.11 ng/mL; P=0.0368). Regarding the maximum temperature, although neither group reached the threshold for low-grade fever, the Tmax of patients in the DDT group (36.6°C) was statistically higher than that in the ET group (36.5°C) (P=0.0239) (Figure 1).

2.2 Host Immunodeficiency and High-Risk Background for Invasive Fungal Disease

Assessments of the host immunodeficiency background and the susceptibility risk for invasive fungal disease revealed that the distributions of three classic host high-risk factors showed no statistically significant differences between the two groups. Regarding whether the duration of neutropenia reached or exceeded 10 days, the incidence was 24.4% (10/41) in the DDT group and 12.9% (4/31) in the ET group, which did not reach statistical significance (P=0.2227). Regarding the presence of concurrent long-term corticosteroid therapy, the exposure rate was 29.3% (12/41) in the DDT group and 38.7%.

(12/31) in the ET group, demonstrating a balanced distribution (P=0.4001). For a history of systemic immunosuppressant use within 3 months prior to admission, the proportion of patients with this combined risk was 48.8% (20/41) in the DDT group and 51.6% (16/31) in the ET group, showing no statistically significant difference (P=0.8119) (Figure 2).

2.3 Accompanying Clinical Symptoms at the Time of Drug Initiation

Further comparison of active accompanying clinical symptoms at the threshold of triggering systemic antifungal intervention revealed that the proportion of patients with active, documented objective fever at the exact moment of drug administration was 46.3% (19/41) in the DDT group compared to 9.7% (3/31) in the ET group, a

difference that was highly statistically significant (P<0.001). In contrast, no significant intergroup differences were detected in the incidence of non-specific respiratory and gastrointestinal accompanying symptoms, such as radiological signs of concurrent pulmonary infection (24.4% vs. 16.1%, P=0.3927), cough and sputum production (39.0% vs. 25.8%, P=0.2388), and diarrhea (2.4% vs. 6.5%, P=0.5738) (Figure 3).

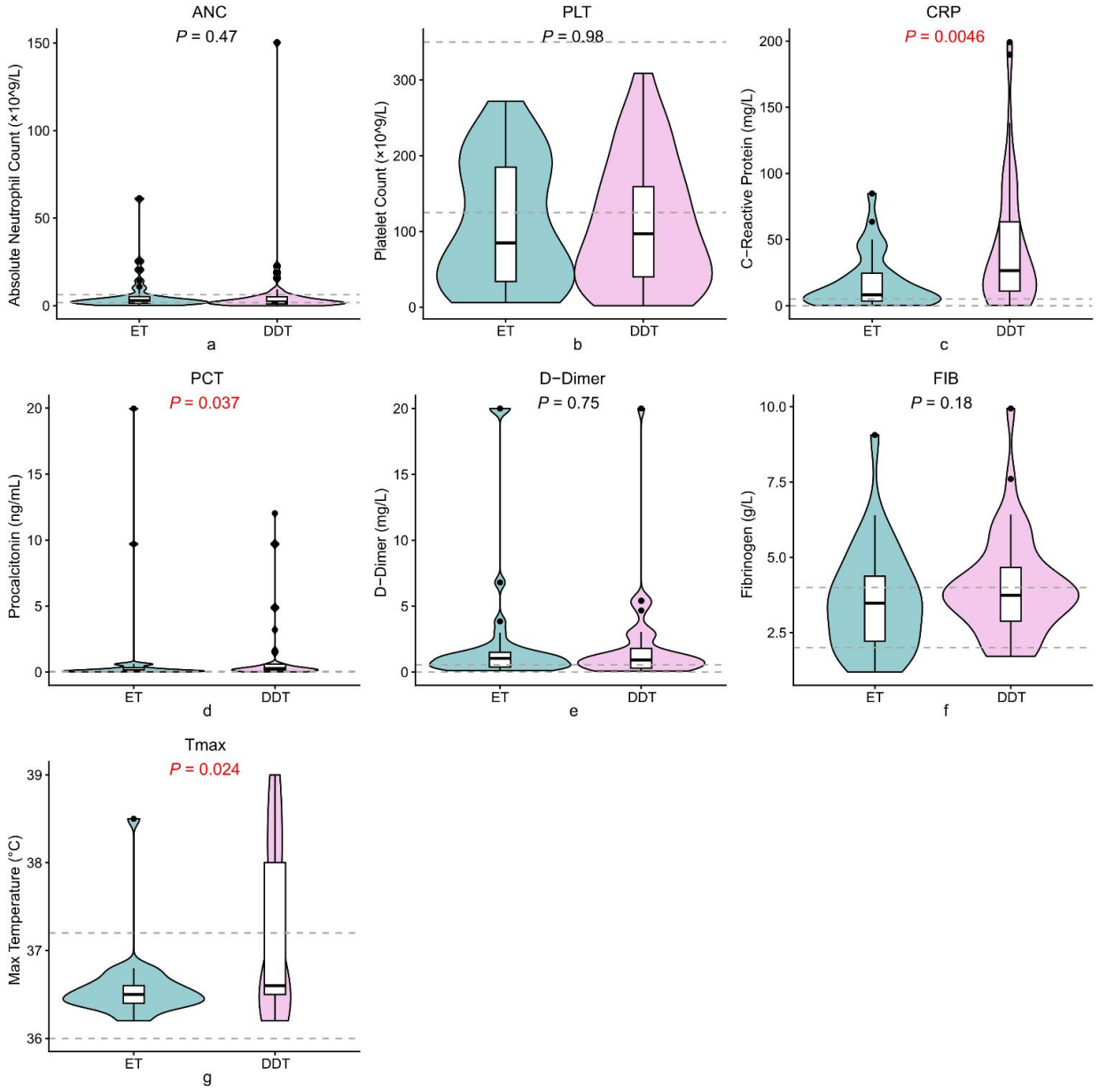


Figure 1. Comparison of baseline laboratory parameters and maximum temperature between the ET and DDT groups at antifungal initiation. Violin plots superimposed with boxplots displaying (a) Absolute Neutrophil Count (ANC), (b) Platelet Count (PLT), (c) C-Reactive Protein (CRP), (d) Procalcitonin (PCT), (e) D-Dimer, (f) Fibrinogen (FIB), and (g) Maximum Temperature (Tmax) recorded within 24 hours prior to antifungal initiation.

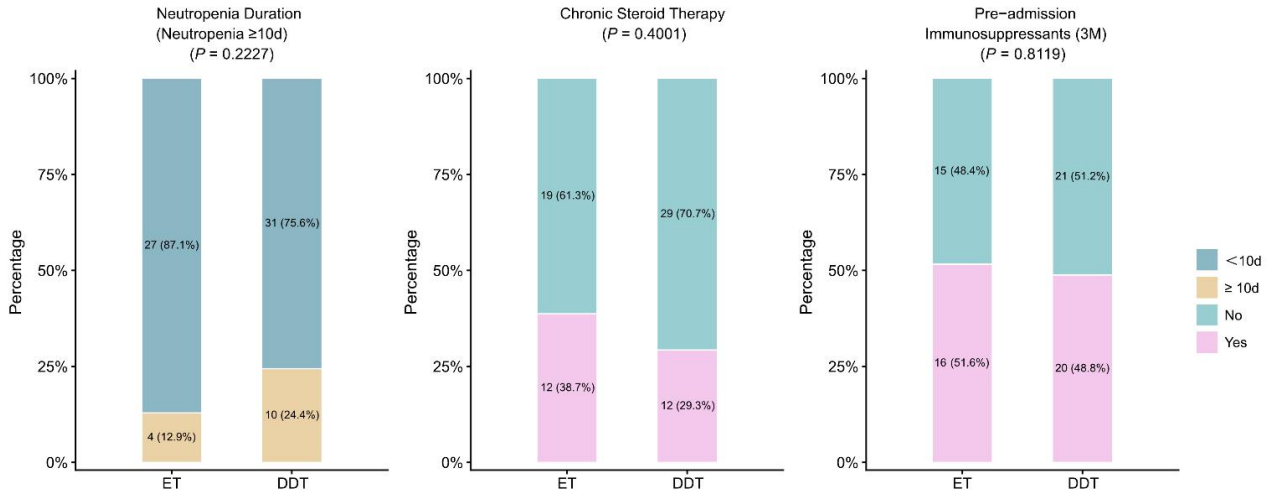


Figure 2. Distribution of baseline clinical risk factors and immunosuppressive history between the treatment cohorts. 100% stacked bar charts detailing the baseline comparability between the ET group (n=31) and DDT group (n=41). (Left) Proportion of profound neutropenia duration (⩾10 days vs. <10 days). (Middle) Prevalence of chronic steroid therapy history (Yes vs. No). (Right) Prevalence of pre-admission immunosuppressant application within the past 3 months (Yes vs. No).

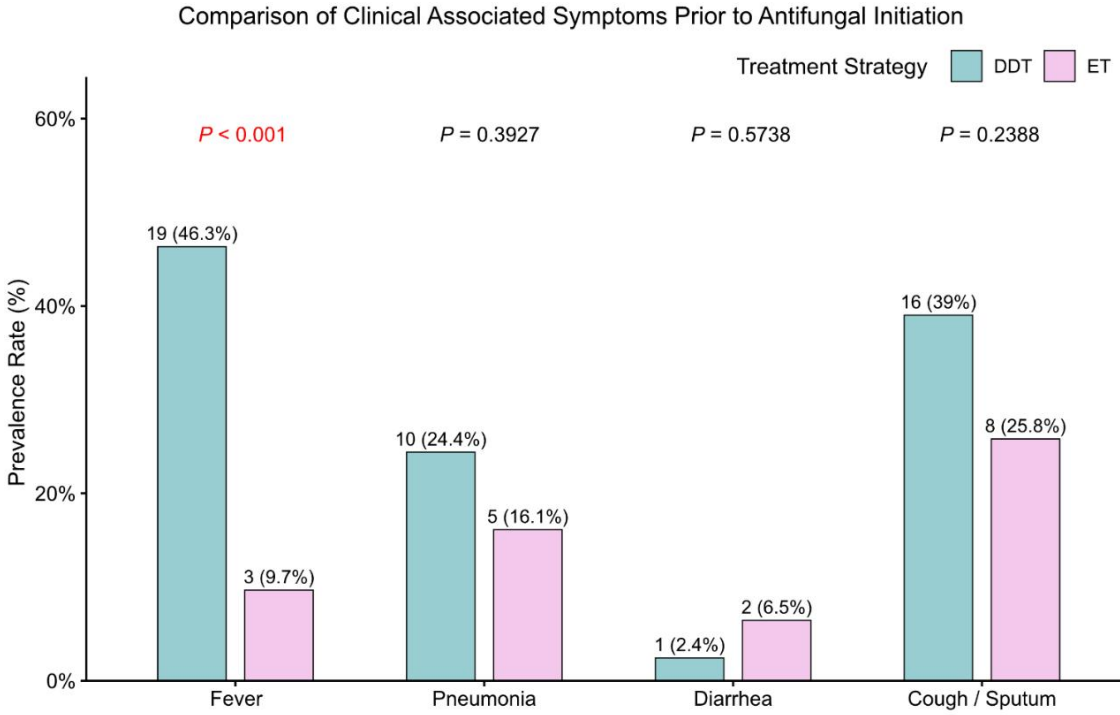


Figure 3. Prevalence rates of clinical associated symptoms prior to systemic antifungal initiation. Grouped bar chart comparing the clinical symptom landscape between the DDT (n=41) and ET (n=31) cohorts at the threshold of starting voriconazole therapy.

2.4 Mycological Biomarker Detection

This study systematically evaluated the qualitative and quantitative characteristics of fungal cell wall components (G/GM assays) at the initiation of systemic antifungal intervention. The results showed that the positivity rate of G/GM assays was significantly higher in the ET group than in the DDT group (45.8% (11/24) vs. 20.5% (8/39); *P*=0.0335). Regarding the quantitative levels of circulating fungal antigens, the quantitative G/GM values in the ET group at the initiation of intervention were also significantly higher than those in the DDT group (*P*=0.0403). These significant differences in both quantitative and qualitative mycological evidence indicate that the two groups presented distinct clinical heterogeneity in their in vivo fungal biological burden at the critical node of triggering systemic antifungal therapy (Figure 4).

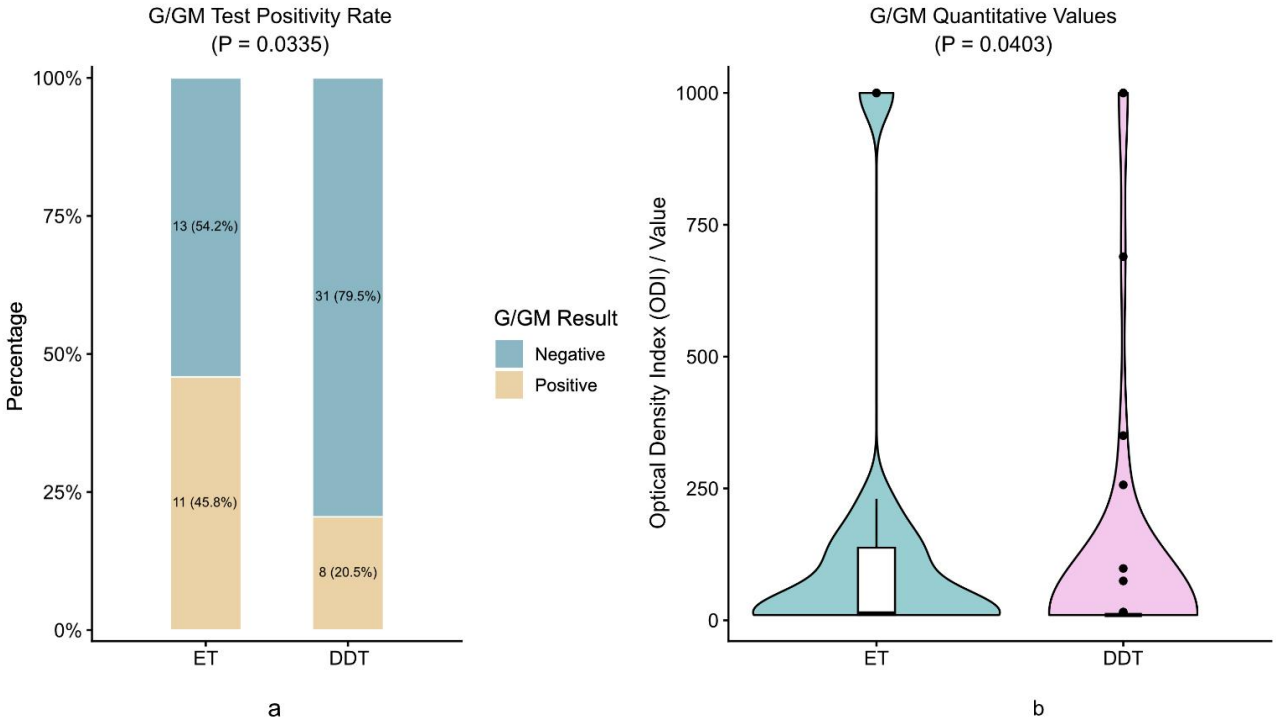


Figure 4. Qualitative positivity and quantitative values of G/GM mycological tests at treatment initiation. (a) 100% stacked bar chart displaying the qualitative G/GM test positivity rate between the evaluable ET (n=24) and DDT (n=39) cases. (b) Violin plots with embedded boxplots illustrating the distribution of G/GM quantitative antigen loads between the two cohorts.

2.5 Clinical Efficacy Outcomes and Intensity of Drug Exposure

Analysis of clinical efficacy outcomes and length of hospital stay showed that the median duration of systemic antifungal therapy was 13 days (IQR: 7–23

days) in the ET group and 10 days (IQR: 7–18 days) in the DDT group, which did not reach statistical significance (P= 0.2593). Regarding the total length of hospital stay, the median duration was 24 days (IQR: 12–34 days) in the ET group and 21 days (IQR: 14–30 days) in the DDT group, which also showed no statistically significant intergroup difference (P=0.7199) (Figure 5).

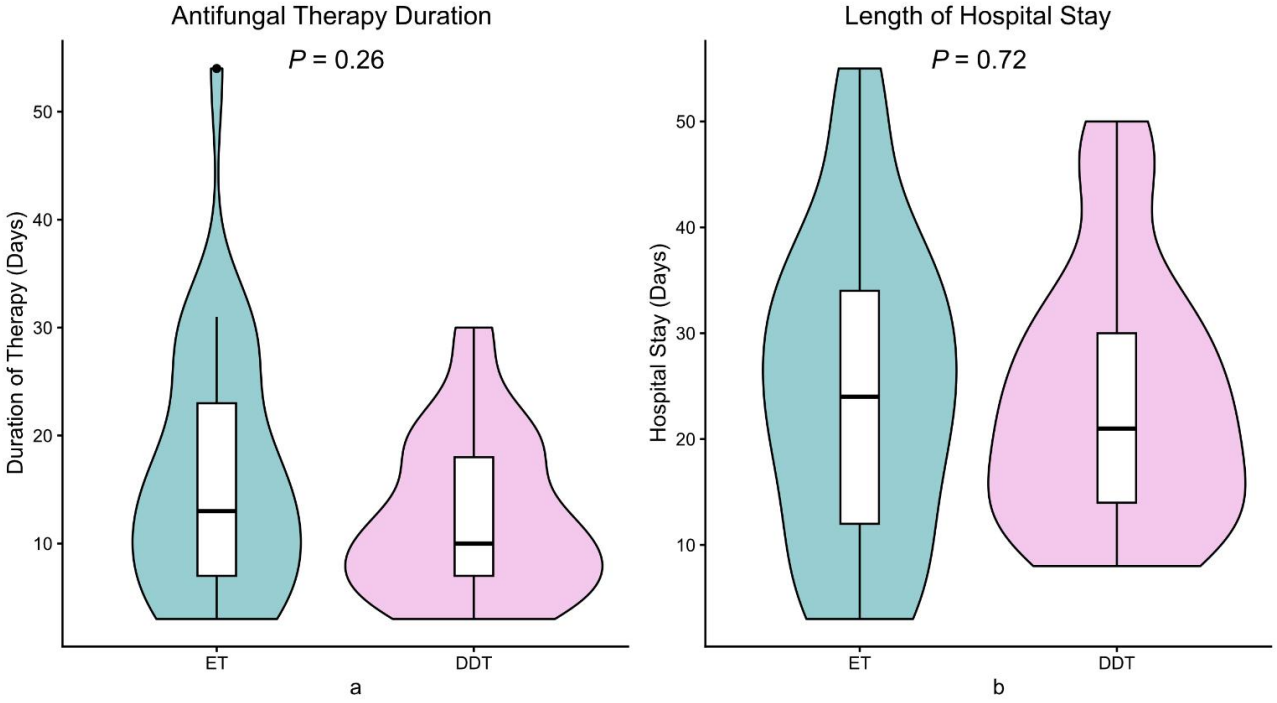


Figure 5. Clinical resource utilization metrics regarding antifungal therapy duration and post-fever hospital stay. Violin plots integrated with boxplots illustrating secondary clinical outcomes across the study cohorts. (a) Total duration of systemic antifungal therapy (days) between the ET and DDT groups. (b) Cumulative length of hospital stay (days) calculated from the onset of the index febrile episode.

2.6 Multivariable Regression Analysis and Clinical Safety Evaluation

To eliminate the interference of clinical confounding factors, a multivariable logistic regression model was established to analyze key safety endpoints, adjusting for case subtype, advanced age (age⩾65 years), history of long-term corticosteroid therapy, and a duration of sustained neutropenia ⩾ 10 days. The regression results demonstrated that, compared with the ET group, the adoption of the DDT strategy was not significantly associated with the risk of IFD events (OR=1.35, 95% CI: 0.33 – 5.42, P=0.6754). Regarding organ toxicity endpoints, no significant differences were observed between the two groups in terms of antifungal drug-induced hepatotoxicity (OR=1.79, 95% CI: 0.31–10.20, P=0.5136) or nephrotoxicity (OR=0.90, 95% CI: 0.28–2.87, P=0.8581) (Figure 6).

2.7 Long-Term Survival and Log-Rank Survival Analysis

As long-term survival prognostic endpoints, Kaplan-Meier survival analysis and the log-rank test demonstrated no statistically significant differences

between the ET and DDT groups regarding the 1-year overall survival rate or IFD-related mortality (P=0.5). During the follow-up period, the survival probability curves of the two groups remained closely interwoven and frequently overlapped throughout the entire disease course (Figure 7).

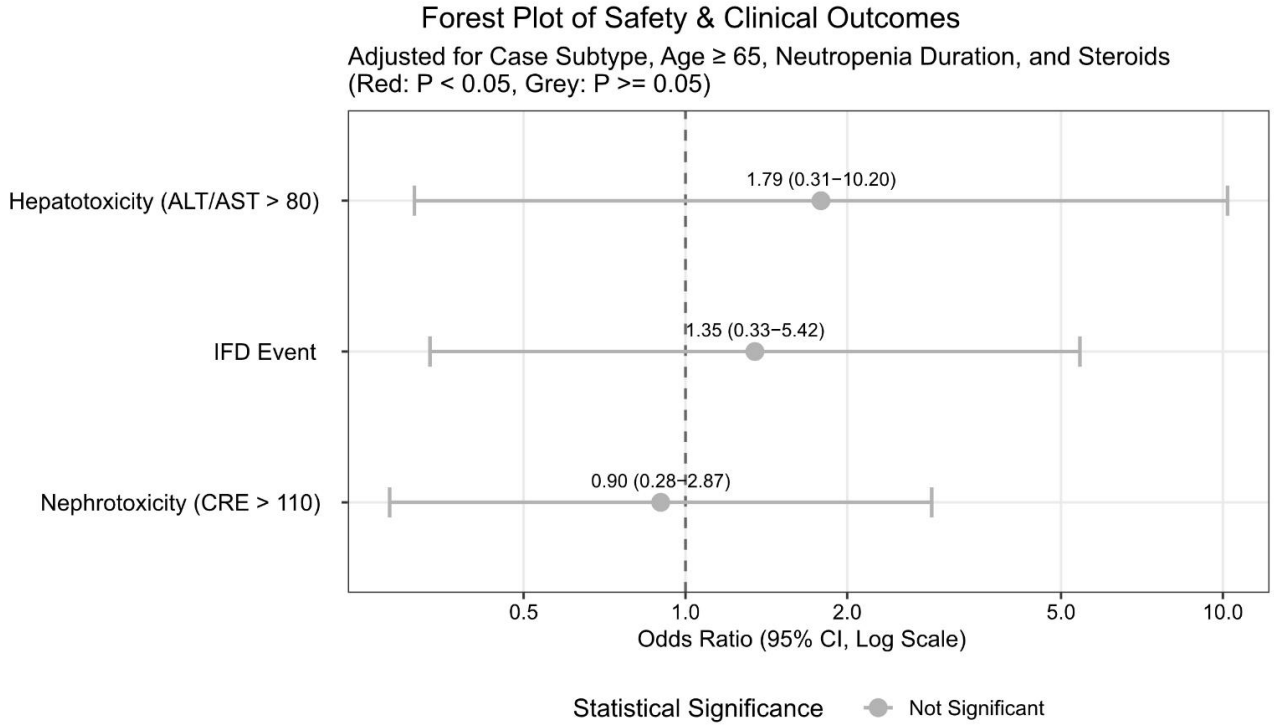


Figure 6. Multivariable logistic regression forest plot evaluating the independent odds ratios for safety and clinical outcomes. Multivariable logistic regression forest plot defining the risk profile of the DDT strategy versus the baseline ET strategy. The analysis model was fully adjusted for essential potential baseline confounders, including primary case subtype, age ⩾ 65 years, deep neutropenia duration, and prior chronic steroid history.

2.8 Roc Curve Analysis of Baseline Inflammatory Indicators for Predicting Long Term Mortality

To further evaluate the early prognostic performance of baseline systemic inflammatory indicators at the initiation of antifungal intervention for predicting 1-year long-term mortality events, ROC curves were constructed and the AUC were calculated. Statistical analysis revealed that the AUC of baseline CRP for predicting 1-year long-term mortality was 0.670. In contrast, the AUC of baseline PCT for predicting 1-year mortality was 0.593, with its predictive curve closely approaching the diagonal random-guess line (Figure 8).

3. Discussion

This study focused on a highly vulnerable population of febrile patients with hematological malignancies or following intensive medical interventions, systematically evaluating the clinical efficacy, safety margins, and prognostic value of

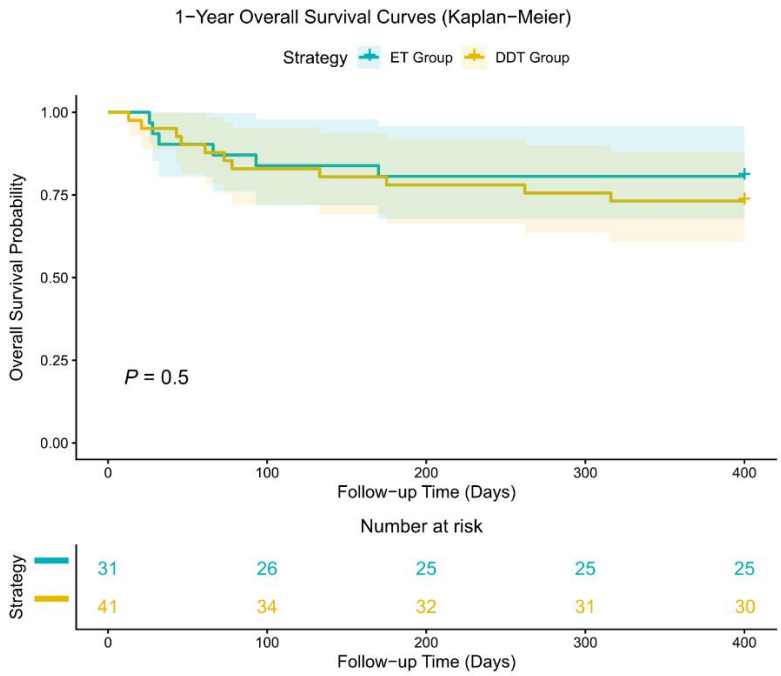


Figure 7. Kaplan-Meier cumulative survival trajectory for 1-year overall survival between the ET and DDT strategies.

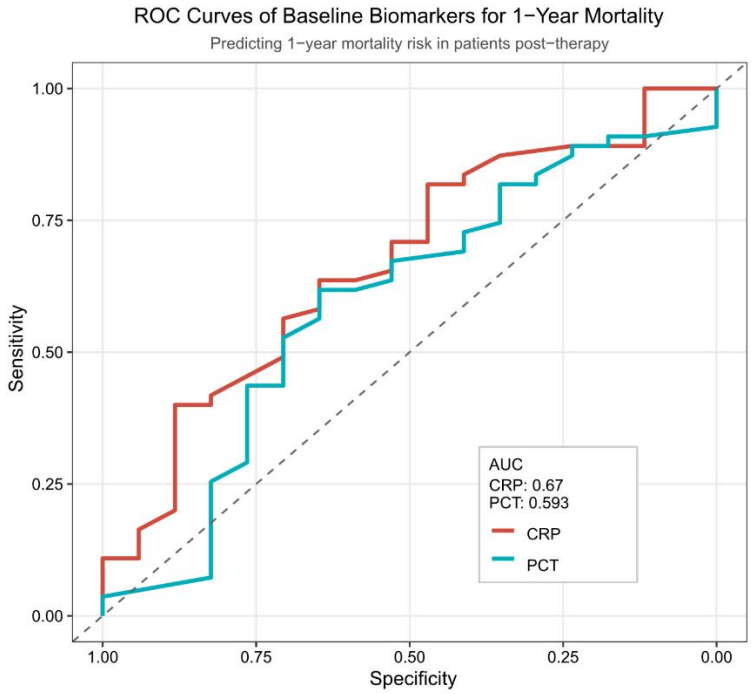


Figure 8. Receiver operating characteristic (ROC) curves of baseline inflammatory biomarkers for predicting 1-year mortality. ROC analysis evaluating the discriminatory performance of systemic inflammatory reactives measured at the specific historical node of antifungal initiation to forecast 1-year post-therapy mortality risk.

under empiric therapy and diagnostic-driven therapy strategies (9). Historically, neutropenic fever following chemotherapy has been associated with high IFD mortality. In traditional clinical practice, due to vigilance regarding the rapid and destructive progression of fungal infections, the ET strategy has long maintained a dominant position. Under this paradigm, systemic antifungal drugs are immediately added when patients experience prolonged neutropenic fever that is refractory to broad-spectrum antibiotics for 4 to 7 days, regardless of definitive microbiological or radiological evidence. However, with the widespread adoption of HRCT, innovations in fungal cell wall component detection technologies, and deep reflection on drug-induced toxicity accumulation and financial burdens, the international and domestic hematology communities are gradually shifting toward the more precision-guided DDT strategy. The core findings of this study not only provide solid evidence-based medical data for this smooth transition to the DDT strategy in real-world clinical practice, but also profoundly deconstruct the intrinsic behavioral heterogeneity of the two strategies during clinical decision-making from the microscopic perspective of multimodal inflammatory biomarkers and mycological dynamics (1).

The primary advantage and foundation of academic self-consistency in this study lies in its rigorous statistical design, which established high homogeneity between the two groups regarding host immunodeficiency background, hematopoietic function recovery, and routine coagulation profiles. In past observational retrospective studies, reviewers frequently raised reasonable concerns that the favorable prognosis or shorter duration of drug therapy in the DDT group might be attributed to clinicians naturally assigning younger "milder patients" without long-term steroid exposure or with shorter neutropenia durations to this group, thereby introducing severe selection bias (10). However, in the present study, the median values of ANC, PLT, D-dimer, and fibrinogen levels were completely comparable between the two groups, and the incidences of prolonged neutropenia, long-term corticosteroid treatment history, and recent immunosuppressant history were also entirely equivalent (1). This highly balanced baseline background ensures that before initiating antifungal intervention, the immune system fragility and potential susceptibility risk for fungal infections were on the exact same starting line for both groups. Therefore, the differences in clinical outcomes observed in this study can be purely attributed to the choice of the therapeutic strategy itself, rather than statistical artifacts caused by confounding factors.

At the critical node of initiating antifungal treatment, the stark contrast between the two groups regarding systemic inflammatory responses, febrile symptoms, and body temperature vividy delineates the behavioral landscape of real-world clinical decision-making. Patients in the DDT group exhibited a significantly elevated median level of clinical inflammatory indicators at the time of drug administration, and the proportion of patients with active objective fever was as high as 46.3%, whereas the proportion of febrile patients in the ET group was only 9.7%. From the perspective of hematology and infectious immunisms, this seemingly paradoxical "febrile proportion inversion" profoundly reveals the

pathophysiological evolution of the two decision-making models in the real world. Patients in the ET group, often in the early stages of their febrile course, may have frequently received corticosteroids, antipyretics, or immunosuppressive interventions, causing macroscopic febrile symptoms to be temporarily masked by medications at the empirical trigger point (11). This protocol-driven or timeline-based drug administration model actually involves a large amount of premature drug exposure when the body's inflammatory cascade has not been truly activated. Conversely, clinicians in the DDT group demonstrated higher evidence-based composure, restraining the impulse for blind drug administration and strictly waiting for the of mycological biomarkers or specific changes in radiological features. During this period, along with the endogenous normal venting of acute-phase reactants triggered by localized fungal activity, patients often accompanied a new round of clear active fever and high inflammatory load when drug administration was truly triggered (11). This decision-making pattern allows clinicians to successfully avoid premature or unnecessary drug exposure due to reactive panic, without compromising clinical vigilance.

The core finding of this study, which possesses the highest clinical explanatory value and academic potential, lies in the "dual significant difference" in both qualitative and quantitative terms presented by circulating mycological biomarkers at the threshold of intervention. Statistical analysis demonstrated that the positivity rate of fungal biomarkers was significantly higher in the ET group than in the DDT group (P=0.0335). More critically, regarding the quantitative level of circulating fungal antigens, the ET group similarly exhibited a significantly higher overload level than the DDT group, with its median quantitative detection value reaching 13.03 (with the upper IQR extending to 137.66), while the DDT group remained at a stable low detection level with a median of 10.00 (P=0.0403). In the past, it was often blindly assumed that because ET is initiated earlier, it could achieve earlier intervention at a lower biological fungal load (11). However, our data forcefully demonstrate that the multimodal close-monitoring framework relied upon by the DDT strategy successfully achieves "prospective interception at the biological level" (2). Because nearly 80% of patients in the diagnostic-driven treatment group still had circulating fungal antigen levels completely at the baseline lower limit of detection at the time of drug administration, this indicates that the vast majority of patients were successfully captured during the subclinical "golden window" of extremely low fungal load before fungal components were released into the bloodstream in large quantities. In sharp contrast, the data from the ET group expose the passivity and lag associated with relying solely on macroscopic refractory fever. By the time patients finally met the traditional empiric therapy criteria for prolonged fever, nearly half of them already accompanied extensive systemic fungal antigen degradation and release at the biological level, and some even reached massive quantitative overloads. This suggests that empirical treatment lacking biomarker and radiological navigation appears fast on the surface, but in reality, it may already be in a lagging, passive position regarding fungal biological control, and it is highly

susceptible to incorporating technical false-positive noise brought about by non-infectious confounding factors such as human serum albumin infusions or the application of broad-spectrum amoxicillin-type antibiotics, thereby exacerbating drug abuse (12).

The multivariable logistic regression model and the 1-year survival timeline analysis deconstruct and eliminate core concerns regarding the safety of the DDT strategy. In populations with hematological malignancies or receiving immunotherapy, the greatest fear among clinicians when delaying systemic antifungal drugs is whether waiting for objective evidence will delay the condition, thereby leading to outbreaks of invasive fungal diseases or increasing the risk of long-term mortality. After fully adjusting for all core clinical confounding factors, including advanced age, malignancy subtypes, history of long-term corticosteroid therapy, and the duration of sustained neutropenia, our regression model demonstrated that the risk of IFD under the diagnostic-driven treatment strategy was highly equivalent to that of the ET group, and the risks of antifungal drug-related hepatotoxicity and nephrotoxicity were also completely within the same safety tier. Furthermore, the 1-year overall survival curves of the two groups were closely interwoven and frequently overlapped during the 365-day follow-up period, with the log-rank test showing absolute non-inferiority and equivalence (P>0.05). Supported by robust dynamic biomarker surveillance and multimodal close clinical monitoring, the strategic waiting implemented to gather definitive evidence possesses flawless non-inferiority regarding long-term survival prognosis compared with traditional blind empirical coverage. Combined with the favorable trend in the diagnostic-driven group showing a 3-day reduction in both the median duration of antifungal therapy and the total length of hospital stay, this strategy demonstrates substantial clinical benefit and pharmacoeconomic value (13,14). It significantly reduces the cumulative organ toxic load on vulnerable patients while substantially saving direct medical expenditures and medical resource consumption.

Finally, by constructing ROC curves for baseline inflammatory biomarkers at the initiation of treatment to predict 1-year long-term all-cause mortality, this study provides a novel perspective on exploring the macroscopic link between acute-phase systemic inflammation and long-term host survival outcomes. The analysis results indicate that at the antifungal starting point, CRP demonstrated moderate and highly credible prognostic recognition value for 1-year mortality (AUC reaching 0.670), which was significantly superior to PCT, a traditional indicator highly specific to severe bacterial infections (AUC of 0.593). In febrile cohorts within hematology departments or following high-dose interventions, the inflammatory storms faced by patients are often intertwined with factors such as mucosal barrier damage after chemotherapy and tissue necrosis during prolonged bone marrow suppression phases (15-17). Because the biological release mechanism of PCT is relatively blunt toward non-infectious systemic inflammatory responses, it is difficult for it to sensitively map long-term complex systemic multiorgan failure outcomes. Conversely, CRP, as an acute-phase reactant protein extremely sensitive to macrophage activation and non-infectious tissue damage, can more

comprehensively and faithfully reflect the patient's overall systemic organ inflammatory environment load in the early stages (18). This finding reminds clinicians that while utilizing CRP and PCT to guide immediate anti-infective drug adjustments, a significantly elevated baseline CRP should be interpreted as a critical baseline warning signal for evaluating long-term adverse survival outcomes, suggesting that clinicians need to strengthen long-term follow-up and close monitoring after patient discharge.

4. Limitations and Perspectives

Although this study completed high-quality causal inference through a rigorous statistical design and multi-modal indicator linkage, several inherent limitations remain to be addressed and expanded upon in future research. First, the present study is constrained by its retrospective, single-center design framework and a relatively modest sample size. These factors may inherently limit the broader generalizability of our findings to diverse clinical settings with varying fungal epidemiology or institutional protocols. Notably, this limited scale likely contributed to the fact that while a favorable target toxicity-reducing trend was observed—wherein the DDT group showed a 3-day median reduction in both the duration of antifungal therapy and total hospital stay—it failed to cross the threshold of statistical significance. Therefore, further large-scale, multicenter prospective clinical trials, particularly randomized controlled trials (RCTs), are urgently warranted to rigorously validate the efficacy, safety margins, and universal applicability of this precise interceptive strategy. Such future endeavors will provide higher-level evidence-based medicine to support its widespread clinical implementation and further establish the macroscopic pharmacoeconomic value of the DDT strategy in optimizing medical resource allocation and reducing direct medical expenditures.

Second, with the widespread clinical popularization of novel targeted small-molecule drugs, the pathophysiological mechanisms of fever in hematological tumor patients are becoming increasingly complex, and non-infectious immune-related adverse events are frequently interwoven and overlapping with early invasive fungal infections. Although this study confirmed that baseline CRP possesses superior long-term mortality warning potential compared with procalcitonin, a single acute-phase indicator remains insufficient for the specific differential diagnosis of complex etiologies in the acute phase. Future research should be dedicated to introducing next-generation multi-omics combined monitoring technologies, including peripheral blood metagenomic next-generation sequencing (mNGS), dynamic tracking of multiplex microfluidic cytokine expression profiles, and artificial intelligence-assisted analysis of microscopic evolutions in chest HRCT radiomics (19,20). By constructing a multidimensional panoramic digital model covering 'host inflammatory load-microbial genetic dynamics-radiological feature evolution,' clinicians are expected to accurately target and identify fungal colonization, active infection, and non-infectious inflammation within an earlier window. This will not only thoroughly drive the advancement of antifungal

intervention in hematological malignancies from the existing 'diagnostic-driven' to a higher-order 'forward-looking predictive-driven' paradigm, but also tailor individual infection prevention and control schemes that balance safety boundaries with ultimate precision for critically ill hematology patients in states of extreme immune fragility.

5. Conclusions

Based on real-world clinical practice, this retrospective study systematically confirms that implementing the DDT strategy in febrile patients with hematological malignancies or following medical interventions offers significant clinical toxicity-reducing advantages and absolute survival equivalence compared with the ET strategy. Statistical evidence demonstrates that under the premise of highly balanced and homogenous baseline bone marrow hematopoietic function, routine coagulation profiles, and classic host immunodeficiency backgrounds between the two groups, the DDT group successfully converged the positivity rate of G/GM assays to a reasonable range more consistent with true epidemiological probabilities by combining clinical symptoms, systemic inflammatory loads, and multimodal biomarkers for precise targeted management. This effectively filtered out technical false-positive decision-making noise caused by non-infectious factors in traditional empirical treatment.

More importantly, after fully adjusting for core confounding factors such as case subtype, advanced age, history of long-term steroid therapy, and the duration of sustained neutropenia, the multivariable regression model and Kaplan-Meier survival analysis jointly established the outstanding safety of the DDT strategy. Postponing the introduction of systemic antifungal drugs until definitive microbiological or radiological evidence is available did not increase the risk of invasive fungal diseases, did not worsen the patients' hepatic or renal organ tolerance load, and achieved statistically equivalent outcomes completely consistent with empiric therapy regarding the 1-year overall survival rate and IFD-related mortality. Furthermore, this study reveals for the first time that the baseline highly sensitive inflammatory indicator CRP at the initiation of treatment possesses significantly superior prognostic recognition efficiency for predicting long-term adverse outcomes across a 1-year span in hematological febrile cohorts compared with procalcitonin, which is specific only to severe bacterial infections. This provides clinicians with a highly valuable early baseline warning biomarker for evaluating patients' long-term organ load and survival outcomes. In conclusion, the diagnostic-driven treatment strategy is a scientific approach that combines precision medicine characteristics with favorable pharmacoeconomic benefits, providing solid evidence-based medical evidence for avoiding blind drug administration and practicing precision infection-attenuated medical care in febrile populations with hematological malignancies at the cohort level.

Declaration

1) ***Consent to publication***

Not applicable.

2) ***Ethical approval and consent to participants***

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by the Institutional Review Board and Medical Ethics Committee of Shenzhen Nanshan People's Hospital. Due to the retrospective nature of the study and the absolute utilization of de-identified and anonymized clinical data, the requirement for written informed consent was formally waived by the Ethics Committee.

3) ***Disclosure of conflict of interests***

Not applicable.

4) ***Funding***

This study was supported by Nanshan District medical key discipline construction financial support project, Shenzhen Nanshan District Health System Science and Technology Major Project (No. NSZD2023018), Hospital-level Research Project of Shenzhen Nanshan People's Hospital (No. YN2025003), NHC Key Laboratory of Nuclear Technology Medical Transformation (Mianyang Central Hospital) (No.2023HYX033 and No.2025HYX005).

5) ***Availability of data and material***

The minimal dataset necessary to interpret, replicate, and build upon the findings reported in this article is not publicly archived in an open repository due to institutional data governance regulations and strict patient privacy protections. However, the de-identified datasets analyzed during the current study are available from the corresponding author upon reasonable academic request.

6) ***Authors' Contributions***

LS: Conceptualization, clinical data collection, statistical analysis, data visualization (plotting), and drafting of the original manuscript. LXX and HMX: Study design, methodology protocol validation, project administration, and critical revision of the manuscript. GZ: Clinical supervision, resource provisioning, structural validation, and final approval of the version to be published. All authors have read and approved the final version of this manuscript.

7) ***Acknowledgement***

The authors express their sincere gratitude to the entire clinical, laboratory, and nursing staff of the Department of Hematology at Shenzhen Nanshan People's Hospital for their exceptional dedication to patient care, rigorous maintenance of electronic medical databases, and technical assistance during this investigation.

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