Efficacy of Caspofungin in Unclassified Invasive Fungal Infection Cases: A Retrospective Analysis of Patients with Hematological Malignancies in China

Background: The management of invasive fungal infection (IFI) is challenging in immunocompromised patients who do not fully satisfy the EORTC/MSG diagnostic criteria of proven or probable IFI. Our study assessed caspofungin efficacy in 582 Chinese patients with hematological malignancies exhibiting unclassified signs or symptoms of IFI.

Material/Methods: This retrospective study included caspofungin treatment outcomes of an unclassified group A (n=401) of patients without microbiological or biomarker results and group B (n=181) patients with positive microbiological or biomarker results. Factors that correlated with clinical outcomes were determined using univariate and multivariate analyses.

Results: Cough (41.8%), expectoration (29.6%), and chest tightness (14.6%) were the most common clinical features, and changes in CT images (88.1%) were more frequently detected than in X-ray images (19.6%) in all patients. Favorable response rates for caspofungin as first-line treatment were 58.2% for group A and 56.3% for group B. Eastern Cooperative Oncology Group (ECOG) score, cardiovascular disease, hemoptysis, and absolute neutrophil count (ANC) <1000/mm³ before antifungal treatment without recovery were associated with unfavorable clinical outcome (P<0.05 for all). Cough and ANC recovery >1000/mm³ were significantly associated with favorable (complete or partial resolution) outcome.

Conclusions: Caspofungin was effective for treating unclassified IFIs of immunocompromised patients. Cardiovascular disease, ECOG score, cough, and/or hemoptysis, as well as ANC count, represent a potential index for estimating response of unclassified IFI patients to caspofungin treatments.

MeSH Keywords: Antifungal Agents • Fruiting Bodies, Fungal • Hematologic Neoplasms

Abbreviations: IFI – invasive fungal infection; ECOG – Eastern Cooperative Oncology Group; ANC – absolute neutrophil count; EORTC – European Organization for Research and Treatment of Cancer; MSG – Mycoses Study Group of the National Institute of Allergy and Infectious; IDSA – Infectious Diseases Society of America; CT – computed tomography; GM – galactomannan; HSCT – hematopoietic stem cell transplantation; OR – odds ratio; CI – confidence interval

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Background

Invasive fungal infection (IFI) is a major cause of morbidity and mortality in patients who are immunocompromised, such as those with hematological malignancies or neutropenia due to anticancer chemotherapy or immunosuppression in human stem cell transplantation [1–3], with IFI manifesting primarily as pulmonary disease. Delays in treatment of IFI contribute to poor prognosis [4–6], but early detection of IFI is often confounded by variability in clinical presentation and a lack of optimal diagnostic criteria [7].

In 2008, the Consensus Group formed by the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group of the National Institute of Allergy and Infectious Diseases (MSG) revised the criteria for defining the proven, probable, and possible diagnostic categories for IFI [8]. Nevertheless, the current guidelines for the management of IFI are inadequate for unclassified IFI cases. Beside the classification into possible, probable, and proven IFIs, categorizations into the groups A, B, C, D, and E, in which patients of the group A have no signs of infection and group B patients develop only persistent febrile neutropenia, whereas group D comprise the probable and group E the proven cases with clear medication indications, have been proposed. Group C has been divided into C-I to C-IV subgroups, and group IV including the possible cases [9] (Supplementary Table 1). However, these revisions failed to address the lack of medical evidence-based guidelines for the diagnostic-driven interventions in the B and C-I, C-II, and C-III unclassified categories, which do not meet EORTC/MSG criteria [10]. Furthermore, the absence of clear, objective diagnostic criteria for these categories confounds the interpretation of the findings of clinical drug trials of antimicrobials for IFI management because only patients meeting the definitions of possible (C-IV), probable, and proven IFI are included in intervention groups [7].

In previous studies, approaches for the treatments of IFIs in patients with hematological malignancies have been proposed, in which the treatments are guided only by risk factors reported in previous studies for specific hematological malignancies [11] and another study indicated that febrile neutropenia alone should be an indication for empirical or pre-emptive antifungal therapies [12]. Given the difficulty clinicians face in obtaining definitive radiological or laboratory evidence for possible IFI diagnosis, effective diagnostic-driven interventions in unclassified cases is critical for the prevention of IFI progression. As a result, physicians might wish to use a pre-emptive antimicrobial therapy for the treatment of unclassified IFI cases that do not fully satisfy the diagnostic EORTC/MSG criteria [9,10,13].

Caspofungin is an echinocandin, which specifically inhibits fungal 1,3-β glucan synthase, thereby compromising the fungal cell wall integrity [14], and it is recommended as empirical therapy in febrile neutropenic patients [15].

A recent Chinese large-scale, observational study of antifungal therapy in hematological diseases revealed that in 1401 patients undergoing hematopoietic stem cell transplantation (HSCT), the most common medications for invasive fungal diseases were triazoles (mainly fluconazole) and echinocandins [16] and a Chinese guideline for treatment of invasive fungal infection after burn injury recommends azoles and candins as first-line treatment for empirical therapies and excludes polyenes for prophylaxis [17]. Another guideline for the management of candidiasis from the Infectious Diseases Society of America (IDSA) recommends caspofungin and azoles as first-line treatments when azole resistance is unlikely [18]. However, caspofungin has fewer drug interactions and adverse effects than triazoles and polyene [19–21] antymycotics, though it has usage limitations in China due to cost-related issues [13]. Caspofungin as a first-line treatment for proven, probable, and possible IFI cases has been reported to have favorable response rates of 56.5% to 66.7% [22–24] when caspofungin was used alone, and favorable response rates of 56.3% to 62.5% when it was used in combination therapy with voriconazole [22,23].

Because there is little information about unclassified IFI evidence-based medications and there is no guideline concerning different subclasses of unclassified IFIs, we conducted this research in order to strengthen the current guidelines for the effective management of unclassified IFIs in immunocompromised patients who fail to satisfy the EORTC/MSG diagnostic criteria for possible, probable, or proven IFI, and we retrospectively performed a multicenter, observational study in China to evaluate the efficacy of caspofungin in hematological patients with unclassified IFI.

Material and Methods

This retrospective, single-arm, multicenter (11 institutions), observational study of the efficacy of caspofungin in 704 immunocompromised patients with hematological malignancies was conducted in China from April 2014 to January 2015. Our study was performed according to the International Conference on Harmonization guidelines on Good Clinical Practice and the Declaration of Helsinki (2004) and was approved by the Ethics Committee of each participating institution. Written informed consent was obtained from each patient prior to our study. Patients’ medical charts were reviewed, and those meeting the current EORTC/MSG diagnostic criteria for proven, probable, or possible IFI were excluded from our study, while the remaining patients were categorized as unclassified IFI cases. In the present study, the unclassified cases were divided into group A (n=401) and group B (n=181). Both groups had
clinical pulmonary symptoms (cough, chest tightness, hemoptysis, expectoration, chest pain, or dyspnea) and radiographic signs consisting of infiltrates and shadows not concordant with current EORTC/MSG diagnostic criteria. Patients without microbiological or biomarker results were assigned to group A, while patients positive for biomarkers and with positive microscopic examination or positive sputum culture were assigned to group B [25].

Treatments and definition of treatment responses

All included patients received caspofungin as mono- or combination therapy for ≥7 days. Other treatments are listed in Table 1. Complete response (CR) was defined as resolution of all attributable symptoms and signs of pulmonary infection and radiological abnormalities. Partial response (PR) was defined by a substantial reduction of attributable symptoms and signs of pulmonary infection and radiological abnormalities (>50%). Stable disease (SD) was defined as minimal or no reduction of attributable symptoms and signs of pulmonary infection and radiological abnormalities. Failure was defined as worsening of pre-treatment signs and symptoms of pulmonary infection or radiological abnormalities. Favorable response was defined as complete or partial response. Unfavorable response was defined as SD, failure, or death due to any cause. Caspofungin efficacy was evaluated after ≥7 days of caspofungin monotherapy or combination therapy with any other antifungal agent.

Microbiology factor evidences to diagnose IFI

Samples were obtained from needle aspiration or biopsy, pleural liquid, BALF, bronchial brush, and sputum, as well as peripheral blood, and used for cytological identification, direct microscopy, or culture and other indirect tests, including galactomannan antigen (GM-test) and β-D-glucan (G-test) tests.

Statistical analyses

The statistical analysis was performed using the SPSS, version 13.0, software (IBM, Armonk, NY, USA). Descriptive analyses of the patient characteristics and clinical data were performed, with the analysis of treatment outcome stratified based on diagnostic group and treatment regimen. Univariate and multivariate analyses were performed to identify factors associated with favorable outcome in the overall patient sample (A and B groups). The level of statistical significance for the various analyses was set at $P<0.05$.

Results

Of the 704 hematology patients evaluated, 122 of them received a diagnosis of proven, probable, or possible IFI according to the current EORTC/MSG diagnostic criteria. Of the remaining 582 unclassified IFI cases, 401 (68.9%) patients were assigned to the A group and 181 (31.1%) patients were assigned to the B group.

The mean age of the study sample was 46.1±16.4 years, and 356 (61.2%) of the patients were men (Table 1). Hematological malignancies included acute myelocytic leukemia, acute lymphoblastic leukemia, non-Hodgkin’s lymphoma, multiple myeloma, aplastic anaemia, myelodysplastic syndrome, acute promyelocytic leukemia, chronic myelogenous leukemia, and chronic lymphocytic leukemia. Most (81.8%) of the patients had Eastern Cooperative Oncology Group (ECOG) scores of 0 to 2.

Hematopoietic stem cell transplantation was used for 13.2% and antinecancer chemotherapy for 33.3% of the patients, whereas 53.4% of them had undergone immunosuppressive, anti-infection or symptomatic and supportive care, and a few other secondary treatments.

Although most of the patients (54.2%) were mildly neutropenic (ANC=1000 to 1500/mm$^3$) before caspofungin treatment, 35.1% of them were severely neutropenic before treatment. However, group A and B only had significant difference in their HSCT origin and the numbers of patients with antibiotic therapy in the previous 2 weeks or fungal infection in the previous 6 months, but the patients in group A had no microbiology findings (Table 1).

Cough, chest tightness, and expectoration were the most common clinical features, occurring in 41.8%, 14.6%, and 29.6% of the overall patient sample, respectively. Changes in computed tomography (CT) images (513) were much more common than changes in chest radiographs (114), occurring in 88.1% versus 19.6% of the overall patient sample, respectively. Marker tests revealed that of the tested patients (n=52), 67.3% were positive for galactomannan (GM) and (n=117) 85.5% for (1–3)-β-D-glucan (G). Positive germ-free sites and other side cultures were positive in 39.8% of the group B patients (Table 2).

In the analysis of caspofungin efficacy, the rates of favorable outcomes were 57.0% for all caspofungin regimens, including 58.6% in group A and 53.6% in group B, and 57.7% favorable outcomes rate for caspofungin as first-line combination therapy, including 56.7% for first-line monotherapy and 65.1% for the first-line combination therapy. Interestingly, the favorable outcomes as first-line monotherapy (51.9%) seemed to be lower than favorable outcomes as first-line combination therapy (90%) in group B patients, but the difference was not significant ($P=0.3073$) due to the small sample size. Similar results of favorable outcome rates were obtained with caspofungin as salvage therapy whether used as mono- or combination therapy. However, these results suggest that caspofungin was effective for treating unclassified IFI cases (Table 3).
### Table 1. Characteristics of patients with unclassified invasive fungal infection.

| Variable                        | Group A     | Group B     | Total   | P-value |
|---------------------------------|-------------|-------------|---------|---------|
| **Case distribution**           | 401 (68.9%) | 181 (31.1%) | 582     |         |
| Female                          | 158 (39.4)  | 68 (37.6)   | 226 (38.8) | 0.9953 |
| Male                            | 243 (60.6)  | 113 (62.4)  | 356 (61.2) |         |
| Age (y)                         | 45.5±16.7   | 46.7±15.8   | 46.1±16.4 | 0.1852 |
| BMI (kg/m²)                     | 18.9±16.6   | 18.9±8.6    | 18.9±14.6 | 0.9570 |
| **Haematopathy**                |             |             |         |         |
| Acute myelocytic leukaemia      | 164 (40.9)  | 80 (44.2)   | 244 (41.9) |         |
| Acute lymphoblastic leukaemia   | 83 (20.7)   | 24 (13.3)   | 107 (18.4) |         |
| Non-Hodgkins lymphoma           | 32 (8.0)    | 15 (8.3)    | 47 (8.1)   |         |
| Multiple myeloma                | 26 (6.5)    | 13 (7.2)    | 39 (6.7)   |         |
| Aplastic anaemia                | 28 (7.0)    | 14 (7.7)    | 42 (7.2)   | 0.6135 |
| Myelodysplastic syndrome        | 37 (9.2)    | 15 (8.3)    | 52 (8.9)   |         |
| Acute promyelocytic leukaemia   | 7 (1.8)     | 5 (2.8)     | 12 (2.1)   |         |
| Chronic myelogenous leukaemia   | 8 (2.0)     | 8 (4.4)     | 16 (2.7)   |         |
| Chronic lymphocytic leukaemia   | 2 (0.5)     | 1 (0.6)     | 3 (0.5)    |         |
| Other malignancies              | 14 (3.5)    | 6 (3.3)     | 20 (3.4)   |         |
| **ECOG score**                  |             |             |         |         |
| 0–2                             | 323 (80.5)  | 153 (84.5)  | 476 (81.8) | 0.2493 |
| 3–4                             | 78 (19.5)   | 28 (15.5)   | 106 (18.2) |         |
| **Comorbidities**               |             |             |         |         |
| Endocrine                       | 37 (9.2)    | 24 (13.3)   | 61 (10.5)  | 0.1415 |
| Cardiovascular                  | 61 (15.2)   | 31 (17.1)   | 92 (15.8)  | 0.5577 |
| Respiratory                     | 29 (7.2)    | 8 (4.4)     | 37 (6.4)   | 0.1981 |
| Urogenital                      | 9 (2.2)     | 5 (5.2)     | 14 (2.4)   | 0.7057 |
| Renal                           | 20 (5.0)    | 7 (3.9)     | 27 (4.6)   | 0.3520 |
| Gastroesophageal                | 15 (3.7)    | 2 (1.1)     | 17 (2.9)   | 0.0805 |
| Hepatic                         | 41 (10.2)   | 14 (7.7)    | 55 (9.5)   | 0.3419 |
| Other gastrointestinal disorders| 2 (0.5)     | 2 (1.1)     | 4 (0.7)    | 0.4125 |
| Others                          | 50 (12.5)   | 13 (7.2)    | 63 (10.8)  | 0.0574 |
| **Treatments**                  |             |             |         |         |
| HSCT                            | 48 (12.0)   | 29 (16.0)   | 77 (13.2)  |         |
| Chemotherapy                    | 132 (32.9)  | 62 (34.3)   | 194 (33.3) | 0.7147 |
| Other interventions             | 221 (55.1)  | 90 (49.7)   | 311 (53.4) |         |
| Immunosuppressive therapy       | 13 (2.2)    | 5 (0.9)     | 18 (3.1)   |         |
| Anti-infection therapy          | 144 (24.8)  | 66 (11.3)   | 210 (36.1) |         |
Of the 582 patients with unclassified IFIs, 58 patients died, from which 32 (5.5%) cases were unrelated to the IFIs (cerebral hemorrhage, intracranial hemorrhage, renal failure and gastrointestinal bleeding) and 26 (4.47%) were related to the IFIs.

All of the variables presented in Table 1 and the radiological/clinical symptoms presented in Table 2 were subjected to univariate analysis to identify those associated with favorable clinical outcome (Supplementary Table 2), and those that demonstrated a significant association were included in the multivariate analysis. The results of the multivariate analysis showed that OR values were 0.54 (0.35–0.85), \( P=0.0076 \) for ECOG scores, 0.56 (0.35–0.89), \( P=0.0140 \) for cardiovascular disease and 0.26 (0.10–0.72), \( P=0.0098 \) for hemoptysis.

### Table 1 continued. Characteristics of patients with unclassified invasive fungal infection.

| Variable                                | Group A | Group B | Total | P-value |
|-----------------------------------------|---------|---------|-------|---------|
| Symptomatic and supportive care         | 56 (9.6)| 16 (2.7)| 72 (12.4)|        |
| Other secondary treatments              | 9 (1.5) | 3 (0.5) | 12 (2.1) |        |
| HSCT type                               |         |         |       | 0.2166  |
| Autograft                               | 8 (16.7)| 2 (6.9) | 10 (13.0)|        |
| Allograft                               | 40 (83.3)| 27 (93.1)| 67 (87.0)|        |
| HSCT cell origin                        |         |         |       |         |
| Bone marrow and peripheral blood        | 19 (39.6)| 20 (69.0)| 39 (50.6)| 0.0125  |
| Peripheral blood and others             | 29 (60.4)| 9 (31.0)| 38 (49.4)|        |
| Chemotherapy type                       |         |         |       |         |
| Intravenous                             | 127 (96.2)| 59 (95.2)| 186 (95.9)| 0.7314  |
| 0.0000                                 |         |         |       |         |
| 1.0000                                 |         |         |       |         |
| Antibiotic therapy previous 2 weeks    | 338 (84.3)| 164 (90.6)| 502 (86.3)| 0.0404  |
| Fungal infection previous 6 months     | 72 (18.0)| 31 (17.1)| 103 (17.7)| 0.0481  |
| Total parenteral nutrition              | 41 (10.2)| 14 (7.8) | 55 (9.5) | 0.3615  |
| Central vein catheter                   | 108 (38.7)| 171 (61.3)| 279 (47.9)| 0.0580  |
| ANC before antifungal therapy           |         |         |       |         |
| ANC <500/mm\(^3\)                       |         |         |       |         |
| ≤7 days                                 | 59 (44.7)| 36 (50.7)| 95 (46.8) | 0.4133  |
| >7 days                                 | 73 (55.3)| 35 (49.3)| 108 (53.2) |        |
| ANC recovery, No                        | 56 (31.1)| 21 (36.5)| 77 (32.8) | 0.3858  |
| ANC recovery, Yes                       | 124 (68.9)| 54 (63.5)| 178 (67.2) |        |
| ANC >1000/mm\(^3\) before antifungal therapy | 220 (55.0)| 94 (52.5)| 314 (54.2) |        |
| ANC <1000/mm\(^3\) before antifungal therapy with recovery | 124 (31.0)| 54 (30.2)| 178 (30.7) | 0.5842  |
| ANC <1000/mm\(^3\) before antifungal therapy without recovery | 56 (14.0)| 31 (17.3)| 87 (15.0) |        |

Values are reported as mean ± standard error or the number of observations and percentage. ECOG – Eastern Cooperative Oncology Group; ANC – absolute neutrophil count; HSCT – haematopoietic stem cell transplantation.
which suggested that these factors were associated with reduced favorable response to caspofungin. Cough, absolute neutrophil count (ANC) >1000/mm$^3$ before antifungal therapy, and ANC <1000/mm$^3$ before antifungal therapy with recovery after treatment (versus ANC<1000/mm$^3$ before antifungal therapy without recovery) were significantly associated with improved clinical outcome in unclassified IFI cases following caspofungin treatment (Table 4).

These results suggest that an index based on ECOG score, cardiovascular disease, cough, and/or hemoptysis might be useful for identifying unclassified IFI cases who will respond favorably to caspofungin monotherapy and combination therapy regimens. Cough was a beneficial factor, whereas elevated ECOG score and prolonged low ANC counts, as well as hemoptysis and cardiovascular diseases, were unfavorable factors.

Table 2. Clinical symptoms, radiological data, and microbiology findings for patients with unclassified invasive fungal infection.

| Clinical data          | Group A (n=401) | Group B (n=181) | Total (n=582) |
|------------------------|-----------------|-----------------|---------------|
| **Clinical symptoms**  |                 |                 |               |
| Cough                  | 159 (39.7)      | 84 (46.4)       | 243 (41.8)    |
| Chest Tightness        | 54 (13.5)       | 31 (17.1)       | 85 (14.6)     |
| Hemoptysis             | 13 (3.2)        | 6 (3.3)         | 19 (3.3)      |
| Expectoration          | 117 (29.2)      | 55 (30.4)       | 172 (29.6)    |
| Chest Pain             | 11 (2.7)        | 3 (1.7)         | 14 (2.4)      |
| Dyspnoea               | 34 (8.5)        | 15 (8.3)        | 49 (8.4)      |
| **Changes in CT**      |                 |                 |               |
| Yes                    | 348 (86.8)      | 165 (91.2)      | 513 (88.1)    |
| New infiltration       | 348 (86.8)      | 165 (91.2)      | 513 (88.1)    |
| **Changes in chest X-ray** |             |                 |               |
| Yes                    | 71 (17.7)       | 43 (23.8)       | 114 (19.6)    |
| Nodule                 | 2 (0.5)         | 1 (0.6)         | 3 (0.5)       |
| Patch shadow or effusion| 38 (9.5)       | 33 (18.2)       | 71 (12.2)     |
| Cavity                 | 0 (0)           | 0 (0)           | 0 (0)         |
| Pleural effusion       | 12 (3.0)        | 7 (3.9)         | 19 (3.3)      |
| Others                 | 27 (6.7)        | 9 (5.0)         | 36 (6.2)      |
| **Microbiology findings** |             |                 |               |
| GM test (n=52) positive | N/A            | 35 (67.3)       | 35 (67.3)     |
| G test (n=117) positive| 0 (0.0)         | 100 (85.5)      | 100 (85.5)    |
| Germ-free sites culture (n=582) positive | 0 (0.0) | 7 (3.9) | 7 (1.2) |
| Other sites culture (n=582) positive | 0 (0.0) | 65 (35.9) | 65 (11.2) |

Discussion

We retrospectively evaluated the efficacy of caspofungin treatment in a cohort of unclassified IFI cases in China who did not satisfy the EORTC/MSG diagnostic criteria for proven, probable, or possible IFI. To the best of our knowledge, this is the first Chinese study to examine caspofungin efficacy in this patient subpopulation, although the EORTC/MSG definitions are not meant to be used to guide clinical practice [8]. A French study including hematological malignancies, HSCT recipients, and neutropenic patients revealed 25% unclassified IFD cases at the beginning of the study, with a 12-week mortality rate of 12%, which was close to that of possible IFD patients [26]. Another Chinese study on unclassified IFDs in leukemia patients similarly reported a mortality rate of 11.3% [27], which is close to our study with 10% overall and 4.47% IFI-related mortalities.
The univariate and multivariate analyses of our study suggested that an index consisting of ECOG score, cardiovascular disease, cough, and hemoptysis might be useful for identifying unclassified IFI cases who will respond favorably to caspofungin treatment. Factors associated with higher ECOG score, cardiovascular disease, respiratory, hepatic disease, chest tightness, treatment types except HSCT and chemotherapy, as well as hemoptysis, might be expected to be associated with unfavorable clinical outcomes, while cough, ANC <1000/mm³ before antifungal therapy with recovery after treatment and ANC >1000/mm³ before antifungal therapy were associated with favorable response of unclassified IFI patients to caspofungin treatment. Previous studies of possible, probable, and proven IFI in immunocompromised patients have found that ANC

| Variable/group                        | Case distribution (%) | Duration (days)  | Favorable response (%) | P-value (favorable response) |
|---------------------------------------|-----------------------|------------------|------------------------|-----------------------------|
| **All caspofungin regimens**          |                       |                  |                        |                             |
| Group A                               | 401 (68.9)            | 12.8±16.1        | 235 (58.6)             |                             |
| Group B                               | 181 (31.1)            | 15.2±13.8        | 97 (53.6)              | 0.2582                      |
| Total                                 | 582                   | 13.5±15.5        | 332 (57.0)             |                             |
| **Caspofungin first-line therapy**    |                       |                  |                        |                             |
| Group A                               | 256 (74.6)            | 12.8±13.9        | 149 (58.2)             |                             |
| Group B                               | 87 (25.4)             | 17.3±17.5        | 49 (56.3)              | 0.7589                      |
| Total                                 | 343                   | 13.6±14.8        | 198 (57.7)             |                             |
| **First-line monotherapy**            |                       |                  |                        |                             |
| Group A                               | 223 (74.3)            | 12.7±14.3        | 130 (58.3)             |                             |
| Group B                               | 77 (25.7)             | 17.3±18.3        | 40 (51.9)              | 0.3325                      |
| Total                                 | 300                   | 13.6±15.2        | 170 (56.7)             |                             |
| **First-line combination therapy**    |                       |                  |                        |                             |
| Group A                               | 33 (76.7)             | 13.6±8.4         | 19 (57.6)              |                             |
| Group B                               | 10 (23.3)             | 17.2±12.3        | 9 (90.0)               | 0.0595                      |
| Total                                 | 43                    | 14.6±9.5         | 28 (65.1)              |                             |
| **Caspofungin salvage therapy**       |                       |                  |                        |                             |
| Group A                               | 145 (60.7)            | 13.0±20.8        | 86 (59.3)              |                             |
| Group B                               | 94 (39.3)             | 13.5±9.3         | 48 (51.1)              | 0.2096                      |
| Total                                 | 239                   | 13.2±16.9        | 134 (56.1)             |                             |
| **Salvage monotherapy**               |                       |                  |                        |                             |
| Group A                               | 113 (58.8)            | 13.1±22.2        | 65 (57.5)              |                             |
| Group B                               | 79 (41.2)             | 13.0±7.7         | 42 (53.2)              | 0.5497                      |
| Total                                 | 192                   | 13.1±17.8        | 107 (55.7)             |                             |
| **Salvage combination therapy**       |                       |                  |                        |                             |
| Group A                               | 32 (68.1)             | 12.3±6.8         | 21 (65.6)              |                             |
| Group B                               | 15 (31.9)             | 15.6±14.4        | 6 (40.0)               | 0.0977                      |
| Total                                 | 47                    | 14.0±11.2        | 27 (57.5)              |                             |

Values are presented as the number of observations and percentage or as the median ± interquartile range.
recovery was associated with favorable IFI outcome [28–30]. Despite our finding that ANC recovery (>1000/mm$^3$) was a significant prognostic factor for caspofungin response in unclassified IFI patients, we have also found ANC recovery to be a useful indicator of the status of antifungal treatment in clinical practice, and caspofungin is the currently recommended antimicrobial for treating IFI in neutropenic patients [18]. The association of favorable outcome and cough seems less straightforward. It is possible that coughing may have greater influence on a physician’s assessment of pulmonary involvement due to greater prominence in clinical presentation. Our findings suggest that future studies of these factors as prognostic indicators of caspofungin response might be beneficial with regard to treating unclassified IFI in immunocompromised patients who do not satisfy the EORTC/MSG diagnostic criteria for proven, probable, or possible IFI.

Our findings are subject to certain limitations. Although our IFI cohort included 582 patients, several of the treatment regimen subgroups in the analysis of caspofungin efficacy were much smaller, with only 9 and 1 patients in the favorable and unfavorable outcome groups, respectively, for first-line caspofungin combination therapy (Table 3). Furthermore, it is possible that some of the patients who lacked microbiological data may have had undiagnosed bacterial or viral infections, which would have contributed to an artificially lowered rate of favorable response to caspofungin treatment.

### Conclusions

The overall favorable outcome of caspofungin treatment was 57.0% with 56.7% for first-line monotherapy and 65.1% for first-line combination therapy in hematological malignancy patients with unclassified IFDs. Our finding that cough, ANC count and ANC recovery, cardiovascular disease, ECOG score, as well as hemoptysis, might be a useful index for identifying unclassified IFI cases who will respond to caspofungin monotherapy and combination therapy regimens is clinically noteworthy because it helps to fill the existing gap in the medical evidence-based guidelines for treating unclassified IFI patients.

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### Conflict of interests

None.

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**Table 4. Multivariate analysis to identify factors associated with favourable outcome to caspofungin treatment for unclassified invasive fungal infection.**

| Variable                                      | OR (95% CI)     | P-value |
|-----------------------------------------------|-----------------|---------|
| ECOG score                                    | 0.54 (0.35–0.85)| 0.0076  |
| Cardiovascular disease                        | 0.56 (0.35–0.89)| 0.0140  |
| Cough                                         | 1.91 (1.33–2.73)| 0.0005  |
| Hemoptysis                                    | 0.26 (0.10–0.72)| 0.0098  |
| ANC >1,000/mm$^3$ before antifungal treatment*| 1.91 (1.17–3.13)| 0.0103  |
| ANC <1,000/mm$^3$ before antifungal therapy with recovery after treatment*| 2.35 (1.38–4.03)| 0.0018  |

OR – odds ratio; CI – confidence interval; ECOG – Eastern Cooperative Oncology Group; ANC – absolute neutrophil count. * Compare to ANC<1000/mm$^3$ before antifungal therapy without recovery.)
### Supplementary Tables

#### Supplementary Table 1. Classification of IFDs in patients with hematological malignancies proposed by Maertens et al. (2012) [9].

| Variable                                      | A               | B                              | C                              | D                              | E                              |
|-----------------------------------------------|-----------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Radiological signs and clinical symptoms      | No              | Persistent febrile neutropenia  | No                             | Clinical (any new infiltrate not fulfilling the EORTC/MSG criteria) | Radiological signs on CT (dense, well-circumscribed lesion(s) with or without a halo sign, air-crescent sign, or cavity) | Not considered necessary |
| Mycology results                              | Negative        | Negative                        | Positive biomarker or microscopy or culture | Negative                      | Positive biomarker or microscopy or culture | Positive tissue or specimen from a sterile site |
| Clinical evidence of IFD                      | No              | No                              | No                             | Yes                            | Yes                             | Yes                             |
| Mycological evidence of IFI                   | No              | No                              | Yes                            | No                             | No                              | Yes                             |
| Final diagnosis                               | Unclassified    |                                  | Possible IMD                   | Probable IMD                   | Proven IMD                      |                                  |
| Management                                    | Prophylaxis      | Empirical therapy               | Diagnostic-driven (pre-emptive) therapy | Targeted therapy               |                                  |                                  |

#### Supplementary Table 2. Univariate analysis to identify factors associated with favorable outcome to caspofungin treatment for suspected invasive fungal infection.

| Variable                              | Unfavorable (stable disease or failure) | Favorable (complete or partial) | OR (95% CI) | P-value |
|---------------------------------------|----------------------------------------|---------------------------------|-------------|---------|
| Age (y)                               | 47.5±16.8                              | 45.0±16.1                       | 0.99        | 0.0764  |
| Sex                                   |                                        |                                 |             |         |
| Female                                | 103 (45.6)                             | 123 (54.4)                      | 1.0         | 0.3092  |
| Male                                  | 147 (41.3)                             | 209 (58.7)                      | 1.19        | 0.85–1.67|
| BMI (kg/m²)                           | 18.1±8.3                               | 19.5±17.9                       | 1.01        | 0.99–1.02|
| Haematopathy                          |                                        |                                 |             |         |
| All malignancies                      | 44 (41.1)                              | 63 (58.9)                       | 1.0         |         |
| Acute myelocytic leukaemia            | 109 (44.7)                             | 135 (55.3)                      | 0.87        | 0.55–1.37|
| Acute lymphoblastic leukaemia         | 4 (33.3)                               | 8 (66.7)                        | 1.40        | 0.40–4.93|
| Non-Hodgkins lymphoma                 | 30 (57.7)                              | 22 (42.3)                       | 0.51        | 0.26–1.00|
| Multiple myeloma                      | 2 (66.7)                               | 1 (33.3)                        | 0.35        | 0.03–3.97|
| Aplastic anaemia                      | 6 (37.5)                               | 10 (62.5)                       | 1.16        | 0.39–3.44|
| Myelodysplastic syndrome              | 18 (46.1)                              | 21 (53.9)                       | 0.82        | 0.39–1.70|
| Acute promyelocytic leukaemia         | 0 (0.0)                                | 1 (100.0)                       | >999.99     |         |
| Chronic myelogenous leukaemia         | 12 (25.5)                              | 35 (74.5)                       | 2.04        | 0.95–4.36|

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| Variable                              | Unfavorable (stable disease or failure) | Favorable (complete or partial) | OR (95% CI)     | P-value |
|--------------------------------------|----------------------------------------|---------------------------------|----------------|---------|
| Chronic lymphocytic leukaemia        | 19 (45.2)                              | 23 (54.8)                       | 0.85 (0.41–1.74) | 0.6474  |
| Other malignancies                   | 6 (31.6)                               | 13 (68.4)                       | 1.51 (0.53–4.29) | 0.4355  |
| ECOG score                           |                                        |                                 |                 |         |
| 0–2                                  | 190 (40.3)                             | 284 (59.7)                      | 1.0             |         |
| 3–4                                  | 58 (54.7)                              | 48 (45.3)                       | 0.56 (0.37–0.86) | 0.0073  |
| Comorbidities                        |                                        |                                 |                 |         |
| Endocrine                            |                                        |                                 |                 |         |
| No                                   | 224 (43.0)                             | 297 (57.0)                      | 1.0             |         |
| Yes                                  | 26 (42.6)                              | 35 (57.4)                       | 1.02 (0.59–1.74) | 0.9558  |
| Cardiovascular                       |                                        |                                 |                 |         |
| No                                   | 199 (40.6)                             | 291 (59.4)                      | 1.0             |         |
| Yes                                  | 51 (55.4)                              | 41 (44.6)                       | 0.55 (0.35–0.86) | 0.0090  |
| Respiratory                          |                                        |                                 |                 |         |
| No                                   | 228 (41.8)                             | 317 (58.2)                      | 1.0             | 0.0394  |
| Yes                                  | 22 (59.5)                              | 15 (40.5)                       | 0.49 (0.25–0.97) |         |
| Congenital                           |                                        |                                 |                 |         |
| No                                   | 250 (43.0)                             | 332 (57.0)                      | 1.0             |         |
| Yes                                  | 0 (0.0)                                | 0 (0.0)                         |                 |         |
| Urogenital                           |                                        |                                 |                 |         |
| No                                   | 242 (42.6)                             | 326 (57.4)                      | 1.0             |         |
| Yes                                  | 8 (57.1)                               | 6 (42.9)                        | 0.56 (0.19–1.63) | 0.2841  |
| Renal                                |                                        |                                 |                 |         |
| No                                   | 235 (42.3)                             | 320 (57.7)                      | 1.0             |         |
| Yes                                  | 15 (55.6)                              | 12 (44.4)                       | 0.59 (0.27–1.28) | 0.1800  |
| Gastroesophageal                     |                                        |                                 |                 |         |
| No                                   | 241 (42.6)                             | 324 (57.4)                      | 1.0             |         |
| Yes                                  | 9 (52.9)                               | 8 (47.1)                        | 0.66 (0.25–1.74) | 0.4016  |
| Hepatic                              |                                        |                                 |                 |         |
| No                                   | 218 (41.4)                             | 309 (58.6)                      | 1.0             |         |
| Yes                                  | 32 (58.2)                              | 23 (41.8)                       | 0.51 (0.29–0.89) | 0.0181  |
| Solid tumor                          |                                        |                                 |                 |         |
| No                                   | 247 (42.7)                             | 331 (57.3)                      | 1.0             |         |
| Yes                                  | 3 (75.0)                               | 1 (25.0)                        | 0.25 (0.03–2.41) | 0.2297  |
| Others                               |                                        |                                 |                 |         |
| No                                   | 226 (43.5)                             | 293 (56.5)                      | 1.0             |         |
| Variable                                      | Unfavorable (stable disease or failure) | Favorable (complete or partial) | OR (95% CI)   | P-value |
|----------------------------------------------|----------------------------------------|---------------------------------|---------------|---------|
| Treatment type                               |                                        |                                 |               |         |
| HSCT                                         | 26 (33.8)                              | 51 (66.2)                       | 1.0           |         |
| Chemotherapy                                 | 78 (40.2)                              | 116 (59.8)                      | 0.76 (0.44–1.32) | 0.3263  |
| Other                                        | 146 (47.0)                             | 165 (53.0)                      | 0.58 (0.34–0.97) | 0.0385  |
| HSCT type                                    |                                        |                                 |               |         |
| Autograft                                    | 1 (10.0)                               | 9 (90.0)                        | 1.0           |         |
| Allograft                                    | 25 (37.3)                              | 42 (62.7)                       | 0.19 (0.02–1.56) | 0.1215  |
| HSCT stem cell derived                       |                                        |                                 |               |         |
| Bone marrow + peripheral blood stem cell     | 16 (41.0)                              | 23 (59.0)                       | 1.0           |         |
| Peripheral blood + others                    | 10 (26.3)                              | 28 (73.7)                       | 1.95 (0.74–5.11) | 0.1751  |
| Chemotherapy type                            |                                        |                                 |               |         |
| Intravenous chemotherapy                     | 73 (39.2)                              | 113 (60.8)                      | 1.0           |         |
| Oral                                         | 5 (62.5)                               | 3 (37.5)                        | 0.39 (0.09–1.67) | 0.2037  |
| Antimicrobial therapy during previous 2 weeks |                                        |                                 |               |         |
| No                                           | 30 (37.5)                              | 50 (62.5)                       | 1.0           |         |
| Yes                                          | 220 (43.8)                             | 282 (56.2)                      | 0.77 (0.47–1.25) | 0.2895  |
| Fungal infection during previous 6 months    |                                        |                                 |               |         |
| No                                           | 152 (41.2)                             | 217 (58.8)                      | 1.0           |         |
| Yes                                          | 46 (44.7)                              | 57 (55.3)                       | 0.87 (0.56–1.35) | 0.5285  |
| Unknown                                      | 52 (47.3)                              | 58 (52.7)                       | 0.78 (0.51–1.20) | 0.2582  |
| Total preteral nutrition                     |                                        |                                 |               |         |
| No                                           | 226 (43.0)                             | 299 (57.0)                      | 1.0           |         |
| Yes                                          | 22 (40.0)                              | 33 (60.0)                       | 1.13 (0.64–2.00) | 0.6640  |
| Central vein catheter                        |                                        |                                 |               |         |
| No                                           | 140 (46.5)                             | 161 (53.5)                      | 1.0           |         |
| Yes                                          | 108 (38.7)                             | 171 (61.3)                      | 1.38 (0.99–1.92) | 0.0580  |
| ANC before antifungal therapy                |                                        |                                 |               |         |
| ANC <500/mm³                                 | 87 (42.9)                              | 116 (57.1)                      | 1.0           |         |
| ANC 500–1000/mm³                             | 31 (50.0)                              | 31 (50.0)                       | 0.75 (0.42–1.33) | 0.3227  |
| ANC >1000/mm³                                | 129 (41.1)                             | 185 (58.9)                      | 1.08 (0.75–1.54) | 0.6896  |
| ANC recovery                                 |                                        |                                 |               |         |
| No                                           | 51 (58.6)                              | 36 (41.4)                       | 1.0           |         |
| Yes                                          | 67 (37.6)                              | 111 (62.4)                      | 2.35 (1.39–3.96) | 0.0014  |
| ANC recovery groups                          |                                        |                                 |               |         |
### Unfavorable (stable disease or failure) vs. Favorable (complete or partial) Comparison

| Variable                                      | Unfavorable | Favorable | OR (95% CI)     | P-value |
|-----------------------------------------------|-------------|-----------|-----------------|---------|
| ANC <1000/mm\(^3\) before antifungal therapy without recovery | 51 (58.6)   | 36 (41.4) | 1.0             |         |
| ANC <1000/mm\(^3\) before antifungal therapy with recovery after treatment | 67 (37.6)   | 111 (62.4) | 2.35 (1.39–3.96) | 0.0014  |
| ANC >1000/mm\(^3\) before antifungal therapy | 129 (41.1)  | 185 (58.9) | 2.03 (1.25–3.29) | 0.0040  |

### Symptoms

#### Cough

|   | Unfavorable | Favorable | OR (95% CI)     | P-value |
|---|-------------|-----------|-----------------|---------|
| No | 162 (47.8)  | 177 (52.2) | 1.0             |         |
| Yes | 88 (36.2)  | 155 (63.8) | 1.61 (1.15–2.26) | 0.0055  |

#### Chest tightness

|   | Unfavorable | Favorable | OR (95% CI)     | P-value |
|---|-------------|-----------|-----------------|---------|
| No | 205 (41.3)  | 292 (58.7) | 1.0             |         |
| Yes | 45 (52.9)  | 40 (47.1)  | 0.62 (0.39–0.99) | 0.0454  |

#### Hemoptysis

|   | Unfavorable | Favorable | OR (95% CI)     | P-value |
|---|-------------|-----------|-----------------|---------|
| No | 237 (42.1)  | 326 (57.9) | 1.0             |         |
| Yes | 13 (68.4)  | 6 (31.6)   | 0.34 (0.13–0.90) | 0.0292  |

#### Expectoration

|   | Unfavorable | Favorable | OR (95% CI)     | P-value |
|---|-------------|-----------|-----------------|---------|
| No | 180 (43.9)  | 230 (56.1) | 1.0             |         |
| Yes | 70 (40.7)  | 102 (59.3) | 1.14 (0.80–1.64) | 0.4762  |

#### Chest Pain

|   | Unfavorable | Favorable | OR (95% CI)     | P-value |
|---|-------------|-----------|-----------------|---------|
| No | 243 (42.8)  | 325 (57.2) | 1.0             |         |
| Yes | 7 (50.0)   | 7 (50.0)   | 0.75 (0.26–2.16) | 0.5911  |

#### Dyspnoea

|   | Unfavorable | Favorable | OR (95% CI)     | P-value |
|---|-------------|-----------|-----------------|---------|
| No | 225 (42.2)  | 308 (57.8) | 1.0             |         |
| Yes | 25 (51.0)  | 24 (49.0)  | 0.70 (0.39–1.26) | 0.2352  |

#### Other

|   | Unfavorable | Favorable | OR (95% CI)     | P-value |
|---|-------------|-----------|-----------------|---------|
| No | 216 (42.1)  | 296 (57.8) | 1.0             |         |
| Yes | 34 (48.6)  | 36 (51.4)  | 0.77 (0.47–1.27) | 0.3124  |

#### Patient

|   | Unfavorable | Favorable | OR (95% CI)     | P-value |
|---|-------------|-----------|-----------------|---------|
| C-II | 166 (41.4)  | 235 (58.6) | 1.0             |         |
| C-III | 84 (46.4)   | 97 (53.6)  | 0.82 (0.57–1.16) | 0.2585  |

#### Fungal infections

|   | Unfavorable | Favorable | OR (95% CI)     | P-value |
|---|-------------|-----------|-----------------|---------|
| No | 237 (43.3)  | 310 (56.7) | 1.0             |         |
| Yes | 13 (37.1)  | 22 (62.9)  | 1.29 (0.64–2.62) | 0.4747  |

#### Caspofungin as first-line therapy

|   | Unfavorable | Favorable | OR (95% CI)     | P-value |
|---|-------------|-----------|-----------------|---------|
| No | 105 (43.9)  | 134 (56.1) | 1.0             |         |
| Yes | 145 (42.3)  | 198 (57.7) | 1.07 (0.77–1.49) | 0.6906  |
Unfavorable response was stable disease or treatment failure, and favorable response was complete or partial resolution. Values for unfavorable and favorable response categories are reported as mean ± standard error or the number of observations and percentage.

ECOG = Eastern Cooperative Oncology Group; ANC = absolute neutrophil count; HSCT = haematopoietic stem cell transplantation.

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