Hepatosplenic candidiasis in patients with hematological malignancies: a 13-year retrospective cohort study

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Summary: Over 13 years, more patients with lymphoid malignancies were diagnosed with hepatosplenic candidiasis (HSC). HSC diagnosis remains challenging. First line antifungal therapy relied mainly on azoles and hematological control was the strongest factor associated with survival in HSC.
Abstract

Background: Hepatosplenic candidiasis (HSC) used to be reported in patients with acute myeloid leukemia (AML) without antifungal prophylaxis. The aim was to describe clinical features and outcomes of HSC over the last 13 years in a single French hematology center.

Methods: All patients diagnosed with HSC between 2008 and 2020 were included in a single-center retrospective cohort study. Data were collected from patient charts and HSC were classified according to the 2020 European Organisation for Research and Treatment of Cancer/Mycoses Study Group definitions.

Results: Sixty patients were included, with 18.3% proven, 3.3% probable and 78.3% possible HSC according to 2020 EORTC/MSG classification. Among them, 19 patients were treated for acute myeloid leukemia (AML), 21 for lymphomas, 14 for acute lymphoblastic leukemia (ALL). HSC occurred in 13 patients after autologous stem cell transplantation for lymphoma. At HSC diagnosis, 13 patients were receiving antifungal prophylaxis. Candida colonization was present in 84.2%, with prior candidemia in 36.7% of cases. β-D-glucans was positive in 55.8% and 45.8% of tissue biopsies were contributive. First line antifungal therapy was azoles in 61.7% and steroids were associated in 45% of cases. At three months of follow-up, partial response to antifungal therapy was 94.2%. At last follow-up (mean 22.6 months), 41 patients (68.3%) presented a complete hematological remission and 22 patients were deceased, none because of HSC.

Conclusions: Epidemiology of HSC changed in the last decade with fewer cases occurring in AML setting. A better identification of patients at risk could lead to specific prophylaxis and improved diagnosis.

Key words: hepatosplenic candidiasis; diagnosis; treatment.
Introduction

Hepatosplenic candidiasis (HSC) is a rare complication occurring after a prolonged period of neutropenia, mainly in the context of hematological malignancies. Incidence is unknown and probably underestimated. In patients with acute myeloid leukemia (AML), incidence rate has been reported in varying proportions, from 3% up to 29% and, historically, HSC was rarely diagnosed in patients with lymphoma.

HSC diagnosis may be challenging and relies on clinical, biological and radiological considerations. The revised European Organisation for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria require examination or recovery of yeasts by culture or amplification of fungal DNA from a tissue biopsy or a specimen from a sterile body site for a proven invasive fungal disease, and, for a probable disease, the positivity of (1,3)-β-D-glucans (BDG) in at least 2 consecutive serum samples in a patient with host factors and clinical features. Regarding HSC, histological examination is rarely contributive. Classically, HSC is suspected in the presence of hepatic or splenic target-like lesions on the computed tomography (CT) scan. Although magnetic resonance imaging (MRI) remains the most sensitive radiological tool for HSC diagnosis, enhanced ultrasonography (US) with contrast and positron emission tomography (PET) scan with 18-fluorodesoxyglucose showed encouraging results regarding both the diagnosis and follow-up of patients with HSC. Furthermore, while blood cultures are often negative, dosage of biomarkers in serum such as BDG or mannan antigens and antibodies could allow earlier diagnosis of HSC and be useful to monitor outcome. However, usefulness of these tools for diagnosis purpose has not been investigated in large contemporary cohorts of HSC patients.
HSC treatment relies on antifungal therapy during three to six months \(^{14}\). In the 2010 Infectious Disease Society of America (IDSA) guidelines \(^{15}\) and the 2012 European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines \(^{16}\), fluconazole was recommended as first line therapy whereas liposomal amphotericin B (LAmB) was preferred in critically ill patients. Currently, IDSA and ESCMID societies recommend use of echinocandins or LAmB as first line therapy \(^{15,17}\). Furthermore, case series of small sample size suggested that corticosteroids were associated with improvement in symptoms and inflammatory response in HSC patients \(^{14,18}\). Hence, the optimal treatment strategy for HSC remains unknown.

Finally, it is likely that the profile of patients with HSC evolved in the past decade given that several major changes recently occurred in the field of HSC, such as the availability of new diagnostic tools (biomarkers, positron emission tomography (PET)-scan), the widespread use of antifungal prophylaxis in patients with AML since 2007 \(^{19}\), and the extended empirical antifungal treatment in neutropenic patients \(^{2,20}\). However, no large contemporary cohort study of HSC patients has been reported to date.

The aim of this study was to describe a large cohort of HSC patients over a 13-year period, encompassing epidemiology, diagnosis work-up, treatment and outcomes in this rare disease.
Material and methods

Study design

This is a retrospective cohort study. All patients diagnosed with HSC between 2008 and 2020 and followed at Saint-Louis hospital (Paris, France) were included. Considering the retrospective study design, data collection from pre-existing medical records, and respect for the anonymity of the patients included (referred to as studies ‘Hors Loi Jardé’ in France), no ethical approval or administrative approval was necessary for this study. This study was submitted to the local Data Protection Officer (DPO) and, upon approval, was identified in the hospital study registry. The research was conducted in accordance with the Declaration of Helsinki. Patients were informed that their clinical data could be used, after anonymisation, for research purposes.

Diagnostic of HSC

Patients were included from insurance database code (CIM-10 codes B377, B378 and B379) and medical charts were reviewed to validate HSC diagnosis. We used the 2020 EORTC/MSG definitions, to define proven HSC as the demonstration of yeasts in a normally sterile site; probable HSC, in a patient with host factors, requires clinical criteria, such as the imaging detection of lesions with typical “bull's-eye aspect” in the liver or spleen, as well as mycological findings, following an episode of candidemia within the previous two weeks; and possible HSC is defined by the presence of host factors and radiological findings of small, target-like abscesses (bull's-eye lesions) in the liver or spleen.

Before 2016, dosage of biomarkers (i.e. BDG, Candida Antigen and serology) were not routinely performed. During this period, if a serum at HSC diagnosis was still available, we retrospectively performed these dosages. BDG testing was performed using Fungitell
assay (Cape Cod Diagnostics, Cape Cod, USA) according to the manufacturer’s instructions. BDG was considered positive when >80 pg/mL. Samples were analysed using PLATELIA Candida Ag Plus for antigen testing and PLATELIA™ Candida Ab PLUS (Biorad) for Candida serology. For antigen testing, we used the cutoff of 125 pg/mL to retain positivity and for Candida serology, samples were considered as positive above 10 UA/mL.”

Moreover, in order to evaluate HSC prevalence over the study period, we obtained from insurance database the number of patients who were hospitalized between 2013 and end of 2019 at Saint Louis Hospital for the treatment of hematological malignancies (CIM-10 codes C81-C96). We also evaluated HSC prevalence in selected sub-populations (i.e. AML, lymphoma, ALL).

**Variables definitions**

Data on patient characteristics at baseline, hematologic disease, *Candida* colonization, and type of treatment were collected from medical charts. Neutropenia was defined as a neutrophil count below 500/mm³ and date of first signs of HSC by prolonged fever (≥3 days) despite broad-spectrum antibiotics and no alternative diagnosis. Furthermore, *Candida* colonization was defined as the presence of *Candida* at direct examination or culture of samples from throat, lung, vagina, urine, skin or stools before or at HSC diagnosis.

**Follow-up**

Partial response at three months was defined by a resolution of all clinical and biological signs with imaging studies showing stable size or reduction of size or number of lesions. Complete response was defined as resolution of all clinical and biological signs with imaging studies showing resolved or calcified nodules. Vital status was recorded. Follow-up ended in May 2020.
Statistical analyses

Continuous variables are expressed as mean (standard deviation) and categorical variables as number (%). Survival curves considering overall survival were generated using the Kaplan-Meier method. Then, a proportional hazard Cox regression modeling was used to estimate hazard ratios (HR) and 95% confidence intervals (CI), considering overall survival as the outcome. The model was adjusted for azole administration, use of corticosteroids, age at HSC diagnosis, length of aplasia >1 month (yes versus no), and hematological remission at HSC diagnosis (yes versus no). Proportional hazard assumption was graphically checked. Analyses were two-sided and performed using R software (version 3.6.2).

Results

Patients’ characteristics

Sixty patients diagnosed with HSC between 2008 and 2020 and followed at Saint Louis hospital were included. Patients’ characteristics are reported in table 1. Mean age at diagnosis was 44.5 years (±17.7) and 35 (58.3%) were men. Hematologic diseases were AML in 19 patients (31.7%), lymphoma in 21 (35%), ALL in 14 (23.3%), and others in six patients (bi-phenotypic leukemia in two, chronic lymphocytic leukemia in one, myelodysplastic syndrome [MDS] in two patients and aplastic anemia in one). Overall, 36 patients (60%) had a disease of lymphoid lineage and for lymphoma patients diffuse large B-cell lymphoma accounted for the majority of patients (10 patients, 47.6%). Other types of lymphoma were T-cell lymphoma (4 patients, 19%) Burkitt lymphoma (3 patients, 14.2%), Hogdkin lymphoma and mantle cell lymphoma (2 patients for each). Among these 36
patients, prior to the diagnosis of HSC, 13 lymphoma patients received autologous stem cell transplantation (auto-SCT). Two patients had received allo-SCT prior to HSC diagnosis.

Prevalence of HSC among all hematological patients ranged between 0.4‰ and 4‰ depending on the considered year. Detailed results are presented in the supplementary table.

At HSC diagnosis, 13 patients were receiving an antifungal prophylaxis, including 9 AML patients (posaconazole for 7 of them and voriconazole for the other 2), 3 MDS (posaconazole) and one ALL (caspofungin).

Mean duration of neutropenia before HSC diagnosis was 30.1 days (±32.6). At HSC diagnosis, 14 patients had neutropenia (24.6%). HSC was diagnosed after a first line treatment for 35 (58.4%) patients, after a conditioning regimen for 14 patients (23.3%) and after a rescue treatment for 11 (18.3%) patients.

**HSC diagnosis**

*Candida* colonization was found in 48 patients (84.2%), with two or more Candida species in 50% of cases, either at or before HSC diagnosis. *Candida albicans* was the most prevalent (79.2%), followed by *C. glabrata* (10.4%), *C. krusei* (6.3%), *C. parapsilosis* (2.1%), and *C. tropicalis* (2.1%).

According to 2020 EORTC criteria, HSC was proven in 11 cases (18.3%), probable in 2 (3.3%) and possible in 47 cases (78.3%).

Twenty-two patients presented candidemia before HSC diagnosis (36.7%). Candidemia occurred in eight of 13 patients previously treated with auto-SCT. Mycological findings are presented in table 2.

HSC radiological diagnosis was made by abdominal CT-scan in 48 cases (81.4%), ultrasound in 7 (11.7%), and PET-scan in four (6.8%).
New tools for HSC diagnosis are presented in table 2. Contrast US was performed in 13 patients (21.7%) with a suspicion of HSC and was positive for 11 of them. PET-scan was performed at diagnosis in 36 patients and showed hypermetabolism of liver and/or spleen in 29 cases (80.6%). For mycological criteria, dosage of BDG, Candida serology and Candida antigen were available for 52, 50 and 55 patients, respectively. Dosage of BDG was positive for 29 patients (55.8%). Candida serology and antigen were positive in 18 (36%) and 22 (40%) cases, respectively. Overall, 24 patients (40%) had a tissue biopsy (19 liver, four skin and one spleen). In 11 (45.8%), direct examination (10/11) or molecular analysis (1/11) by multiplex PCR were positive for yeasts. All cultures remained negative. Of note, nine of the eleven contributive biopsies originated from liver biopsies.

Treatment of HSC

As presented in table 1, first line antifungal therapy after HSC diagnosis relied on azoles in 37 patients (61.7%), among which 30 received fluconazole, 5 voriconazole and 2 posaconazole. Caspofungin was used in 22 (36.7%) and LAmB in one patient. Among patients, 35 (58.3%) were treated with the same agent for the whole duration of antifungal therapy. For 17 patients (28.3%), caspofungin was switched to oral treatment depending on microbiological findings. For the remaining patients, treatment was changed due to interaction with treatment, microbiological findings or impossibility of oral administration (3, 3 and 2 patients respectively). Antifungal combination was used for three patients (5%). Corticosteroids were used in 27 patients (45%). Mean duration of curative treatment was 7.4 months (±6.0).
Follow-up

Mean follow-up was 22.6 months (±19.3). At 3 months, response status was available for 52 patients of which 49 were in partial response (94.2%). At last follow-up, complete response was observed in 53 patients (88.3%, table 1). In 25 patients, a PET-scan was performed to evaluate radiological response and a resolution of hepato-splenic hypermetabolism was observed in 21 patients. Furthermore, hematologic treatment was delayed for only eight patients (13.8%) due to active infection or deterioration of general or biological status.

At last follow-up, 41 patients (68.3%) presented a complete hematological remission. Eleven patients (18.3%) received an allogeneic SCT, performed a mean time of 123.6 days (±64.3) after HSC diagnosis. Post-allo-SCT HSC recurrence was diagnosed in one out of these 11 patients.

Overall survival of patients with HSC is represented in figure 1. Overall, 22 patients died during the study period, mainly following disease progression (for 12 of them) but none from HSC. Other causes of death were infectious complications for 7 patients (3 complicated bacteriemia, 2 pneumonitis, 1 arthritis and 1 infection due to Fusarium), metabolic complications, cardiogenic shock and severe graft versus host disease (1 patient each). Overall survival at 3 and 6 months were 88.3% and 81.5%, respectively. As presented in table 3, the absence of hematological remission at HSC diagnosis was associated with an increased risk of overall mortality (HR 3.53, 95% CI 1.13 – 11.03) while there was a borderline association for older age (HR 1.02, 95% CI 1.00 – 1.05).
Discussion

This study provides an updated overview of the epidemiology and outcome of HSC over 13 years in a single site retrospective study. Little is known about the incidence and recent epidemiology features of HSC. HSC was historically mainly described in patients with AML after neutrophil recovery. Since the first HSC descriptions, antifungal prophylaxis has been widely used for patients with AML, with a decreasing incidence of invasive aspergillosis in that setting. However, to our knowledge, the impact of antifungal prophylaxis on the incidence of HSC has not been studied. As compared with a previously published cohort of HSC patients in the early 21st century, fewer patients with AML were diagnosed in our study (31.7% versus 66.7%) and more patients with malignancies of lymphoid lineage (35.0% versus 12.5% of lymphoma patients for instance). Antifungal prophylaxis in patients with AML probably partly explains the shift of HSC diagnoses in our study towards patients with « lymphoid diseases », with only a third of HSC cases diagnosed among patients with AML. In our study, over the 19 patients diagnosed with AML only 9 had received antifungal prophylaxis prior to HSC diagnosis. The generalization of antifungal prophylaxis could reduce further the incidence of HSC in AML patients. Another plausible explanation for this shift is the evolution of chemotherapy for patients with ALL and lymphomas in the past decade. Novel treatments such as immunomodulating and immunosuppressive agents in addition to cytotoxic treatments are associated with an increased risk of invasive fungal infections among these patients. Furthermore, in France, L-Asparaginase has been used since 2005 to treat adult ALL patients and is well known to disrupt the gastrointestinal tract, which might contribute to the development of HSC. Interestingly, 13 patients were diagnosed with HSC after autologous transplantation for lymphomas. Among those patients, eight had a previous candidemia (61.5%), which is a
higher rate than usually observed. Moreover, a direct exam was positive for yeast in only 45.8% of biopsies (11/24). Also, patients presented a rapidly favorable evolution under antifungal treatment. In most previously published studies, reporting a majority of HSC cases occurring in patients with AML, the rate of previous candidemia was around 20-30%, liver biopsies were positive in less than 40%, and the need for adjunctive corticosteroids was around 50%.

Regarding HSC diagnosis, although new diagnostic tools were used, definite diagnosis remains challenging. BDG is now included as a mycologic criteria, in at least 2 consecutive serum samples, for the diagnosis of HSC by the EORTC, with a sensitivity of 77% for yeast infections. Combined mannan-antimannan is also included as a mycologic criteria by European Conference on Infections in Leukemia with a better sensitivity than BDG to detect disseminated candidiasis and is useful as an early marker of HSC. We retrospectively performed, for all patients with available serum, dosage of biomarkers (i.e. BDG, mannan antigen and antibodies). Dosage of BDG was positive for 29 patients (55.8%). Candida serology and antigen were positive in 18 (36%) and 22 (40%) cases, respectively, which are lower than observed in other studies.

Given the study period and considering the fact that dosage of biomarkers were not routinely performed before 2016, we rarely had two successive serum samples to fit the criteria for a probable diagnosis of HSC according to 2020 EORTC/MSG classification. Of note, using only one positive sample for BDG at the time of HSC diagnosis, as it was recommended in the previous 2008 EORTC/MSG classification, we observed 14 probable case (23.3%) and 35 possible (58.4%). As previously reported, candidemia was observed in only 36.7% of cases in our study, but having a candidemia in the two weeks before the appearance of hepatosplenic lesions was still included as a mandatory clinical feature for a
probable diagnosis of HSC in the 2020 EORTC/MSG definition that we used in our study. Regarding radiological diagnosis, CT scan was mostly performed in our study, but we also used PET-scan at diagnosis for 36 patients and for follow-up. New diagnostic tools with a better specificity and sensitivity are mandatory to improve HSC diagnosis.

In our study, the first line treatment of HSC mainly relied on azoles or caspofungin. When compared to a former published study considering patients treated between 2000 and 2007, we report less frequent antifungal combination therapy and less delayed or modified chemotherapy, as recommended by several guidelines and authors. The optimal first line treatment remains debated. Both IDSA and ESCMID societies recommend the use of echinocandins or LAmB as first line therapy. This recommendation is based on the fact that patients are currently receiving more antifungal prophylaxis and thus might have an increased risk of developing infection with an azole-resistant organism. In particular, the use of echinocandins is supported by the results of a recent meta-analysis showing the superiority of echinocandins over amphotericin B and azoles. However, fluconazole as a first line treatment or following LAmB induction has been shown to be effective in some studies, although these date have not been readdressed for 30 years. In our study, first line treatment relied mainly on azoles (61.7% of patients). Considering HSC, at last follow-up, complete response was observed in 88.3% of patients but, given the size of the cohort, analyzing risk factors associated with response was not contributive.

From our study results, neither azoles nor corticosteroids administration improved overall survival. However, due to the small sample size of our study and its non-randomized design, drawing definite conclusions is unwise.
The physiopathology of HSC remains unclear. One main hypothesis is the deregulation of Th1/Th17 and Th2/Treg response after neutrophil recovery leading to an immune reconstitution syndrome as observed for cryptococcosis in acquired immunodeficiency syndrome \(^3,3^5\). This could explain the efficacy of adjunctive corticosteroids for persisting fever despite antifungal treatment. The physiopathology might be different for cases occurring after lymphoid diseases. The CANHPARI study (Hepatosplenic candidiasis: PETscan and immune response analysis), which is an ongoing multicenter prospective pilot study investigating pathogenesis, diagnosis and therapeutic strategies of hepatosplenic candidiasis (https://research.pasteur.fr/fr/project/canhpari/), should soon deliver interesting results and might give new insights on the pathogenesis of HSC \(^3^6\).

This study has several strengths such as the extended recruitment period and the relatively important number of cases in contrast to the paucity of data regarding HSC in the literature. However, our study has some limitation’s. First, serum and PET-scan were not available at diagnostic and follow-up for all patients in order to evaluate new diagnostic tools. Second, we may lack power to detect differences given the sample size and monocentric nature of the study and our results may lack of generalizability. Third, the retrospective observational design of this study precludes any causality assumption or conclusions regarding HSC treatment. Finally, results regarding HSC prevalence should be taken with caution since i) the number of patients seen at the hospital (all hematological patients and for each sub-population) refers to the number of hospitalizations over the considered year and are not strictly the number of diagnoses (i.e. a patient with lymphoma can be hospitalized in 2013 for any reason although the diagnosis was made before) and ii) given the very small number of HSC each year, prevalence rates estimates are prone to high uncertainty.
In conclusion, our study gives an updated overview of the epidemiology of HSC over a 13-year period. More patients with lymphoid diseases were noted when compared with previous reports in which AML patients were predominant, possibly explained by the widespread use of antifungal prophylaxis in AML patients and new therapeutic regimen in lymphoid diseases. In the setting of lymphoid diseases, HSC could represent an emerging invasive fungal infection. This study also revealed less delayed chemotherapy treatment after HSC diagnosis than previously published, and hematological control was the strongest factor associated with survival in HSC. Nevertheless, this rare disease remains a challenge in hematological malignancies and studies exploring the physiopathology of HSC, potentially leading to improve diagnostic tools, are urgently needed, as studies on treatment optimization and prophylaxis.

**Potential Conflicts of Interest**

The authors have declared no conflict of interest.

**Patient Consent Statement**

Considering the retrospective study design, data collection from pre-existing medical records, and respect for the anonymity of the patients included (referred to as studies ‘Hors Loi Jardé’ in France), no ethical approval or administrative approval was necessary for this study. This study was submitted to the local Data Protection Officer (DPO) and, upon approval, was identified in the hospital study registry. The research was conducted in accordance with the Declaration of Helsinki. Patients were informed that their clinical data could be used, after anonymisation, for research purposes.
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# Tables

**Table 1: characteristics of the HSC population**

| Overall population  | N=60 (%)          |
|---------------------|-------------------|
| **Baseline characteristics** |                   |
| Male gender         | 35 (58.3)         |
| Age (years)         | 44.5 ± 17.7       |
| Hematologic disease |                   |
| Acute myeloid leukemia | 19 (31.7)     |
| Acute lymphoid leukemia | 14 (23.3)     |
| Lymphoma            | 21 (35.0)         |
| Others              | 6 (10.0)          |
| Stem cell transplantation prior to HSC diagnosis | |
| None                | 32 (68.0)         |
| Autologous          | 13 (27.7)         |
| Allogenic           | 2 (4.3)           |
| **Characteristics at HSC diagnosis** |                     |
| Candida colonization | 48 (84.2)         |
| Neutropenia duration (days) | 30.1 ± 32.6 |
| Hematologic disease control | 35 (58.3) |
| Prior candidemia    | 22 (36.7)         |
| EORTC/MSG classification |                   |
| Possible            | 47 (78.3)         |
| Probable            | 2 (3.3)           |
| Proven              | 11 (18.3)         |
| **Treatments**      |                   |
| Antifungal prophylaxis | 13 (22.0)       |
| First line antifungal therapy |               |
| None                | 0 (0)             |
| Azoles              | 37 (61.7)         |
| Caspofungine        | 22 (36.7)         |
| Liposomal Amphotericin B | 1 (1.6)   |
| Antifungal therapy combination | 3 (5.0) |
| Duration of curative treatment (months) | 7.4 ± 6.0 |
| Use of corticosteroids | 27 (45.0)          |
| Delayed or modified chemotherapy | 8 (13.8) |
| **Follow-up data**  |                   |
| Follow up (months)  | 22.6 ± 19.3       |
| Partial response at 3 months | 49 (94.2) |
| Complete response at last follow up | 53 (88.3) |
| Hematologic remission at last follow-up | 41 (68.3) |
| Death at last follow-up | 22 (36.7) |

*Note: values are n (%) or mean ± SD.*

*Abbreviations: EORTC/MSG: European Organization for Research and Treatment of Cancer/ Mycoses Study Group.*
Table 2: contribution of diagnostic tests used for HSC.

| Mycological findings                  | N positive/N tested |
|---------------------------------------|---------------------|
| Prior candidemia                      | 22/60               |
| Positive β-D-glucan                   | 29/52               |
| Positive *Candida* serology           | 18/50               |
| Positive *Candida* antigen            | 22/55               |

| Radiologic exams                      |                    |
|---------------------------------------|---------------------|
| Contrast ultrasonography              | 11/13               |
| CT-scan                               | 43/43               |
| PET-scan                              | 29/36               |

| Contributive biopsy*                  | 11/24               |

* examination or recovery of yeasts by culture or amplification of fungal DNA by PCR obtained by biopsy from a sterile body site.

**Abbreviations:** HSC: hepatosplenic candidiasis; CT: computed tomography; PET: positron emission tomography.
Table 3: results of Cox regression modeling for overall survival.

|                                | HR   | 95% CI     |
|--------------------------------|------|------------|
| Azole administration           | 0.70 | 0.28 – 1.71|
| Corticosteroids administration | 1.24 | 0.48 – 3.21|
| Age at HSC diagnosis (per 1 year increase) | 1.02 | 1.00 – 1.05|
| Neutropenia >1 month           | 0.97 | 0.36 – 2.58|
| No hematological remission at HSC diagnosis | 3.53 | 1.13 – 11.03|

Abbreviations: HR: hazard ratio; CI: confidence interval; HSC: hepatosplenic candidiasis.
**Figure legend**

**Figure 1:** Overall survival.

*Note:* Dotted lines represent 95% confidence interval.