Invasive Fungal Infections in Decompensated Cirrhosis: A Clinical Case Series and Its Prognostic Implications

Juan Francisco Maag · Ignacio Roca · Lucía Navarro · Manuel Barbero · Nicolás Domínguez · Omar Galdame · Fernando Cairo

Hepatology & Liver Transplant Unit, Hospital El Cruce de Florencio Varela. Provincia de Buenos Aires, Argentina.

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Summary

Introduction and Objectives. *Systemic fungal infections are an under-recognized cause of morbidity and mortality in patients with decompensated liver cirrhosis. Our goal was to describe the clinical features, microbiological findings, and outcomes of invasive fungal infections in this population in the context of a liver transplant center.* ***Materials and Methods.*** *We conducted a retrospective observational study of 16 adult patients with decompensated cirrhosis and culture-proven invasive fungal infections diagnosed between 2013 and 2024. Data were collected from electronic medical records and microbiology databases. Fungal pathogens were isolated from blood or ascitic fluid cultures. We analyzed demographics, cirrhosis etiology, antifungal treatment, and outcomes.* ***Results.*** *The mean age was 41 years, and 50% of patients were female. All patients had decompensated cirrhosis and a mean model for end-stage liver disease-sodium score of 25.7. Half of them met criteria for acute-on-chronic liver failure at diagnosis. The most frequent isolates were Candida albicans (37.5%) and Cryptococcus neoformans (37.5%). Ascites was present in 87.5% of patients; and 68.8% had received antibiotics, while 31.2% had received corticosteroids, within 30 days prior to diagnosis. In-hospital mortality was 62.5%, with a median survival of 11 days.* ***Conclusions.*** *Invasive fungal infections in decompensated cirrhosis are associated with high short-term mortality and often occur in patients who have been exposed to antibiotics or corticosteroids. Awareness of this complication and prompt initiation of antifungal treatment may improve outcomes. Multicenter studies are needed to define risk factors and optimize diagnostic and therapeutic strategies.*

Keywords. *Cirrhosis, candida albicans, cryptococcus neoformans, model for end-stage liver disease-sodium, acute-on-chronic liver failure, in-hospital mortality.*

Correspondence: *Juan Francisco Maag*
Mail: jfmaag92@gmail.com

Infecciones fúngicas invasivas en la cirrosis descompensada: serie de casos clínicos y sus implicancias pronósticas

Resumen

Introducción y objetivos. *Las infecciones fúngicas sistémicas son una causa poco reconocida de morbilidad y mortalidad en pacientes con cirrosis hepática descompensada. El objetivo de este estudio fue describir las características clínicas, hallazgos microbiológicos y los desenlaces de las infecciones fúngicas invasivas en esta población en el contexto de un centro de trasplante hepático.* ***Materiales y métodos.*** *Se llevó a cabo un estudio observacional retrospectivo de 16 pacientes adultos con cirrosis descompensada e infecciones fúngicas invasivas confirmadas por cultivo diagnosticadas entre 2013 y 2024. Los datos se recopilaron a partir de las historias clínicas electrónicas y las bases de datos de microbiología. Los hongos patógenos se aislaron a partir de hemocultivos o cultivos de líquido ascítico. Se analizaron las variables demográficas, la etiología de la cirrosis, el tratamiento antifúngico y la evolución clínica.* ***Resultados.*** *La edad media fue de 41 años y el 50% de los pacientes fueron mujeres. Todos los pacientes presentaban cirrosis descompensada, con una puntuación promedio en el modelo de enfermedad hepática terminal-sodio de 25,7. La mitad de los enfermos cumplía los criterios de falla hepática aguda sobre crónica en el momento del diagnóstico. Los patógenos más frecuentes aislados fueron Candida albicans (37,5%) y Cryptococcus neoformans (37,5%). El 87,5% de los pacientes presentaba ascitis; el 68,8% había recibido antibióticos y el 31,2% corticosteroides en los 30 días previos al diagnóstico. La mortalidad intrahospitalaria fue del 62,5%, con una mediana de supervivencia de 11 días.* ***Conclusiones.*** *Las infecciones fúngicas invasivas en la cirrosis descompensada se asocian a una elevada mortalidad a corto plazo y suelen ocurrir en pacientes que han estado expuestos a antibióticos o corticosteroides. El conocimiento de esta complicación y el inicio precoz del tratamiento antifúngico pueden mejorar la evolución. Son necesarios estudios multicéntricos para definir los factores de riesgo y optimizar las estrategias diagnósticas y terapéuticas.*

Palabras clave. *Cirrosis, Candida albicans, Cryptococcus neoformans, modelo de enfermedad hepática terminal-sodio, falla hepática aguda sobre crónica, mortalidad intrahospitalaria.*

Abbreviations

CAID: Cirrhosis-Associated Immune Dysfunction.
ACLF: Acute-on-Chronic Liver Failure.
ICU: Intensive Care Unit.
NK: Natural killer.
PCR: Proteína C Reactiva.
EASL: Study of the Liver.
CT: Computed Tomography.
MRI: Magnetic Resonance Imaging.
MELD-Na: Model for End-Stage Liver Disease - Sodium.
SBP: spontaneous bacterial peritonitis.
HCC: Hepatocellular Carcinoma.
AHI: Autoimmune Hepatitis.
HCV: Hepatitis C Virus.
PBC: Primary Biliary Cholangitis
PSC: Primary Sclerosing Cholangitis
IQR: Interquartile Range.
MASLD: Metabolic Dysfunction-Associated Steatotic Liver Disease.

Introduction

Systemic fungal infections have become an increasingly recognized cause of morbidity and mortality in immunocompromised patients.[1, 2] Patients with liver cirrhosis are predisposed to severe infections due to a progressive impairment of immune function known as cirrhosis-associated immune dysfunction (CAID). This immune syndrome is characterized by an initial activation of the innate immune system, followed by immune paralysis that favors opportunistic infections, which are often underdiagnosed.[3, 4]

Recent medical literature reports an incidence of fungal infections in hospitalized cirrhotic patients ranging from 2% to 16%. A higher frequency is observed in those with acute-on-chronic liver failure (ACLF) and multiple organ failure, admission to the intensive care unit (ICU), diabetes, acute kidney injury, prolonged hospital stays, or prior bacterial infections.[5] These infections are often nosocomial in origin and develop following an initial infection, typically in the setting of prolonged antibiotic therapy or treatment failure.[6] Clinical manifestations include fungemia, fungal peritonitis, and fungal pneumonia. Reported mortality rates range from 68% to 79% for certain presentations.[6, 7]

Antibiotic-induced intestinal fungal dysbiosis contributes to the overgrowth of *Candida*, particularly *C. albicans*. This overgrowth has been linked to more severe clinical courses and an increased risk of hospital readmission.[5] The dysbiosis is compounded by the immune dysfunction characteristic of CAID, involving impaired function of neutrophils, monocytes, B and T lymphocytes, and natural killer (NK) cells.[3]

Diagnosing fungal infections in cirrhotic patients remains challenging. Conventional cultures have low sensitivity, and biomarkers such as 1,3-β-D-glucan or galactomannan lack specific validation in this population. Combining them with PCR may improve sensitivity, although important limitations persist.[8]

Despite their significant impact on prognosis, invasive fungal infections in this population have received considerably less attention than bacterial infections. This lack of specific data limits the development of effective early detection strategies and appropriate empirical treatment.

The present study describes the experience of a liver transplant center with systemic fungal infections in patients with decompensated cirrhosis. It characterizes the incidence of these infections, their clinical presentation, microbiological findings, and clinical course. The study emphasizes the need to consider this etiology in the differential diagnosis of patients with clinical deterioration and systemic inflammatory response of unclear origin.

Materials and Methods

A retrospective observational study was conducted at Hospital El Cruce Néstor Kirchner in Buenos Aires, Argentina. This high-complexity public hospital functions as a national referral center for complex diseases and advanced treatments, and has a specialized liver transplantation program. The study included adult patients over 18 years of age who were diagnosed with cirrhosis and developed an invasive fungal infection. An invasive fungal infection was defined as the isolation of fungi from blood or ascitic fluid cultures obtained in a clinically compatible context, between May 2013 and April 2024.

Data were collected from electronic medical records and the microbiology laboratory database. Ascitic fluid samples were processed by inoculating 10 mL into resin-containing blood culture bottles and incubating them at 37°C for five days. The samples were also processed on solid media after centrifugation. When a fungal culture was specifically requested, samples were inoculated onto Sabouraud agar and incubated for up to 21 days. Blood samples were processed using the automated Bactec® system.

Liver cirrhosis was diagnosed based on a combination of clinical, biochemical, histological, and imaging criteria. According to the guidelines of the European Association for the Study of the Liver (EASL), decompensation events were defined as the development of ascitic-edematous syndrome, variceal gastrointestinal bleeding, portosystemic encephalopathy, hepatorenal syndrome, or spontaneous bacterial peritonitis (SBP). Hepatocellular carcinoma (HCC) was diagnosed using the EASL-recommended noninvasive criteria, which rely on the identification of arterial-phase hyperenhancement and portal or delayed venous washout on dynamic imaging (CT or MRI) in patients with cirrhosis.[9]

ACLF was defined according to the EASL Clinical Practice Guidelines for the management of this condition.[10]

Demographic variables, cirrhosis etiology, comorbidities, prior use of antibiotics and corticosteroids, recent surgeries, clinical parameters at admission (MELD-Na, Child-Pugh score, presence of ACLF), microbiological characteristics, antifungal treatment, and clinical outcomes were recorded.

The study was approved by the institutional ethics committee and was conducted in accordance with current regulations and international principles for research involving human subjects.

Statistical Analysis

Continuous variables were expressed as the mean and standard deviation or the median and interquartile range, depending on their distribution. Categorical variables were reported as percentages. A survival curve was constructed using the Kaplan–Meier method. All statistical analyses were performed using R Studio, version 1.4.1717.

Results

Sixteen cases of invasive fungal infection were identified in patients with decompensated liver cirrhosis between 2013 and 2024. These cases were recorded within a cohort of 1,800 patients with decompensated cirrhosis under active follow-up at the center, representing an incidence below 1%. The mean age was 41.1 ± 16 years, and 50% were female. All cases corresponded to decompensated stages, with moderate to severe ascites present in 87.5% of patients. The mean MELD-Na score at diagnosis was 25.7 ± 6.4, and 50% of patients met criteria for ACLF at admission, with a mean CLIF-C ACLF score of 51 points (Table 1).

The most frequent etiology of cirrhosis was autoimmune hepatitis (AHI) (31.2%), followed by HCV (18.8%). (Figure 1) Of the patients, 31.2% had received systemic corticosteroid treatment, and 68.8% had been treated with antibiotics within the 30 days prior to diagnosis.

Of those hospitalized, 56.2% were admitted to the

Table 1. *Population Characteristics (n = 16)*

Age (mean ± SD)	41.1 ± 16.6
Female sex, n (%)	8 (50.0%)
Hepatocellular carcinoma, n (%)	2 (12.5%)
Ascites, n (%)	
– None	2 (12.5%)
– Mild	2 (12.5%)
– Moderate – severe	12 (75.0%)
Encephalopathy, n (%)	9 (56.2%)
HBV, n (%)	1 (6.2%)
PBE, n (%)	0 (0%)
Previous ACLF episodes, n (%)	2 (12.5%)
Diabetes, n (%)	5 (31.2%)
Hypertension, n (%)	3 (18.8%)
Recent abdominal surgery, n (%)	1 (6.2%)
Coronary artery disease, n (%)	2 (12.5%)
Chronic kidney disease, n (%)	2 (12.5%)
Other immunosuppressive conditions, n (%)	4 (25.0%)
HIV, n (%)	1 (6.2%)

intensive care unit, while the remainder was managed in general wards. The median time from admission to diagnosis was 6 days. A total of 81% of patients had a Child-Pugh score of C.

The most frequently isolated fungus was *Candida* spp. (62.5%), with *C. albicans* (37.5%) and *C. parapsilosis* (18.75%) being the most common species, followed by *Cryptococcus neoformans* (37.5%). In 75% of cases, the organism was isolated from blood cultures. A total of 93.75% of isolates were susceptible to both fluconazole and amphotericin (Table 2).

The symptoms leading to patient admission to the center were related to cirrhosis decompensation and signs of infection.

Five patients (31.2%) were discharged, and only 1 patient (6.2%) underwent liver transplantation after successful treatment of the infection. The remaining 10 patients (62.5%) died, with a median survival of 11 days from diagnosis (IQR 8-22) (see Figure 2). All deceased patients had ascites; 80% of which were classified as severe. Seventy percent of patients had received recent antibiotic treatment.

Figure 1. *Etiology of cirrhosis*

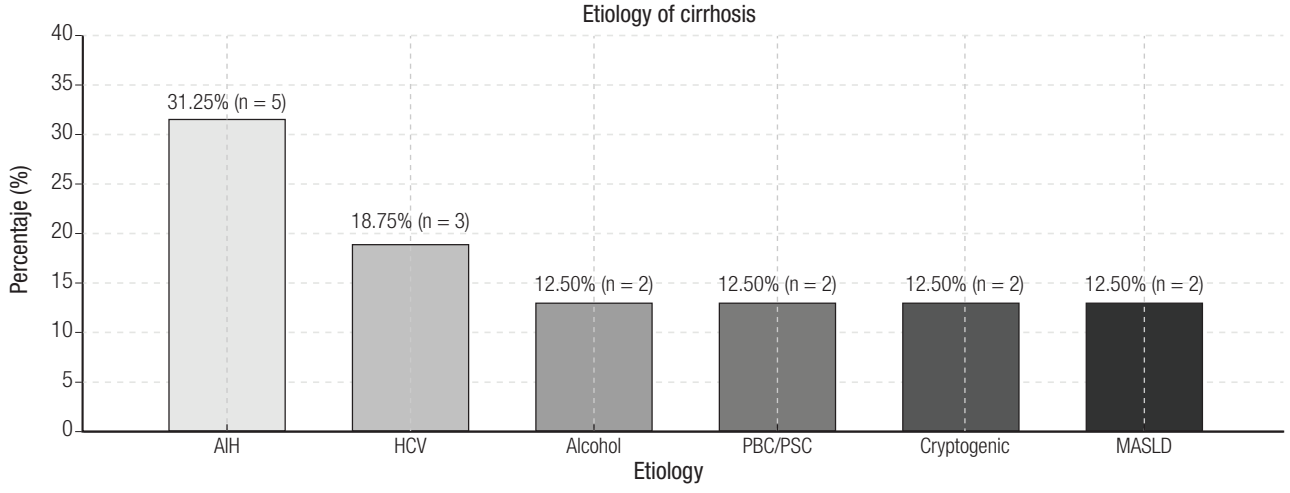
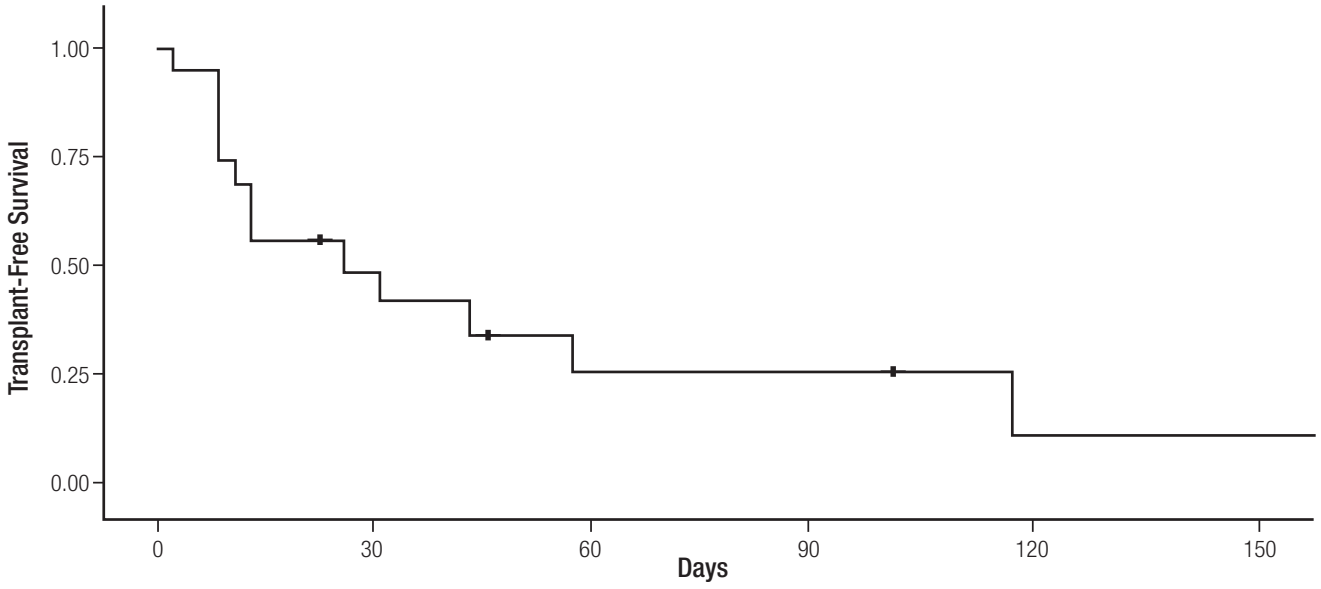


Table 2. *Microbiological isolates*

	Microbiological Isolate			Susceptibility		
	Ascitic Fluid	Blood Cultures	Total (n, %)	Flu	Ampho	Voriconazole
Cryptococcus neoformans	–	6	6 (37.5%)	100%	100%	N/A
Candida spp.						
– *albicans*	4	2	6 (37.5%)	83.33%	83.33%	N/A
– *parapsilosis*	–	3	3 (18.75%)	100%	100%	N/A
– *glabrata*	–	1	1 (6.25%)	100%	100%	N/A

Flu: Fluconazole. **Ampho:** Amphotericin. **N/A:** Not applicable (susceptibility not tested for all isolates).

Figure 2. *Kaplan-Meier Survival Curve*



Discussion

In our study, the incidence of fungal infections in patients with cirrhosis was below 1%, slightly lower than the range reported in the literature of 2% to 10.2%.[11,12] This discrepancy may be explained by underdiagnosis related to the low sensitivity of culture methods and the non-specific clinical presentation of these infections.

In line with the literature, fungal infections predominantly occur in patients with advanced liver disease, with MELD-Na scores generally ranging between 20 and 25. In our cohort, the mean MELD-Na was 26, consistent with these findings. Additionally, 87.5% of patients presented with ascites, reflecting an advanced stage of liver disease.[13, 14, 15]

AIH was the leading etiology (31.2%), and corticosteroid exposure was common in this group, even at low doses. This contrasts with European series, where alcohol-related and viral cirrhosis are more prevalent and steroid exposure is lower (18.3%).[13] In alcoholic hepatitis, corticosteroid use has been identified as a risk factor for invasive fungal infections.[16]

Prior antibiotic use was high (68.8%), consistent with previous studies.[15] This exposure may disturb the intestinal microbiota and promote *Candida* spp. overgrowth, particularly *C. albicans*, as documented by Lahmer *et al.* in patients with severe alcoholic hepatitis.[13]

The observed mortality rate (62.5%) was similar to that reported in other cohorts (73-100%),[13, 14, 15] with a median survival of 11 days, slightly longer than the 8 days reported in previous studies.[13] The high mortality rate and delayed diagnosis among deceased patients underscore the need for continuous clinical vigilance.

Candida albicans and *Cryptococcus neoformans* were the most frequently identified pathogens, showing high susceptibility to both fluconazole and amphotericin B. These findings suggest that either antifungal could represent an appropriate first-line treatment option for suspected fungal infections in our setting.[14]

In Latin America, although data are limited, studies suggest that the incidence and prevalence of autoimmune hepatitis are higher than in other regions of the world.[17] This results in greater corticosteroid exposure among patients with chronic liver disease.

Our findings highlight the importance of implementing early diagnostic strategies and empirical antifungal therapy in at-risk patients and underscore the need for multicenter studies to better characterize these infections in our region.

Our study has the strength of providing one of the few detailed descriptions of invasive fungal infections in decompensated cirrhosis from Latin America. It includes microbiologically confirmed diagnoses and systematic clinical characterization in the setting of a liver transplant referral center. Although limited by its retrospective single-center design, small sample size and selection bias, the study contributes valuable information that underscores the diagnostic challenges and highlights the need for early recognition and treatment of these infections.

Conclusion

Invasive fungal infections are rare but serious complications in patients with decompensated cirrhosis. They are associated with high mortality and significant diagnostic challenges. In our series, these infections were primarily observed in patients with prior exposure to antibiotics or corticosteroids and in those with advanced liver disease. The predominance of *Candida albicans* and *Cryptococcus neoformans*, both susceptible to fluconazole and amphotericin B, suggests that these agents may be appropriate first-line treatments when fungal infection is suspected clinically. Given the limited regional data, multicenter studies are needed to better define the true burden of these infections and improve diagnostic and therapeutic strategies.

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