Clinical characteristics and predictors of mortality in cirrhotic patients with candidemia and intra-abdominal candidiasis: a multicenter study

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Abstract

Purpose: The aim of the study was to describe the characteristics of cirrhotic patients with candidemia and intra-abdominal candidiasis (IAC) and to evaluate the risk factors associated with 30-day mortality.

Methods: A multicenter multinational retrospective study including all consecutive episodes of candidemia and IAC in adult patients with liver cirrhosis in 14 European hospitals during the period 2011–2013 was performed.

Results: A total of 241 episodes (169 candidemia, 72 IAC) were included. Most Candida infections were acquired in hospital (208, 86.3%), mainly in the intensive care unit (ICU) (121, 50.2%). At clinical presentation, fever was seen in 60.6% of episodes (146/241) and septic shock in 34.9% (84/241). *C. albicans* was the most common species (found in 131 episodes, 54.4%), followed by *C. glabrata* (35, 14.5%) and *C. parapsilosis* (34, 14.1%). Overall, the 30-day mortality was 35.3%. Multivariable analysis identified candidemia (OR 2.2, 95% CI 1.2–4.5) and septic shock (OR 3.2, 95% CI 1.7–6) as independent factors associated with 30-day mortality. Adequate antifungal treatment (OR 0.4, 95% CI 0.3–0.9) was associated with survival benefit.

Conclusions: A shift towards increasing prevalence of *C. glabrata* and *C. parapsilosis* species in patients with liver disease was documented. Candidemia and IAC were associated with significant mortality in cirrhotic patients. Thirty-day mortality was associated with candidemia and severe clinical presentation, whereas adequate antifungal treatment improved the prognosis.

Keywords: *Candida*, Invasive candidiasis, Candidemia, Intra-abdominal candidiasis, Cirrhosis

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Take-home message: Cirrhotic patients with invasive *Candida* infections are highly susceptible to septic shock. Thirty-day mortality in cirrhotic patients is associated with advanced liver disease, candidemia, and severe disease at clinical presentation, whereas adequate antifungal treatment improves the prognosis.

Introduction

Advanced liver disease predisposes one to develop severe infections, mainly as a result of cirrhosis-associated immune dysfunction (CAID), that come into play as cirrhosis progresses and is characterized by humoral immunodeficiency, cell-mediated dysfunction, and systemic inflammation [1]. Bacterial infections in cirrhotic patients are common and have been associated with increased risk of mortality [2]. Fungal infections are described as an emerging problem associated with high fatality rates and delayed diagnosis [3]. Previous antibiotic therapy may induce dysbiosis, which may predispose one to alterations in gut microbiota, intestinal dysmotility, and *Candida* spp. overgrowth. This could promote the translocation of fungi to the extraluminal areas, resulting in intra-abdominal infections and further dissemination [4]. In addition to classical intra-abdominal manifestations, such as abdominal abscesses with or without peritonitis, previous studies in cirrhotic patients have shown that *Candida* spp. can be responsible for approximately 10% of bloodstream infections [5] and up to 3.5–6% of spontaneous peritonitis [3, 6].

The aim of the study was to describe the characteristics and outcome of candidemia and intra-abdominal candidiasis (IAC) among cirrhotic patients and to assess the factors associated with mortality.

Materials and methods

Patient population and study design

A retrospective multicenter multinational cohort study was performed in 14 hospitals across Europe (Italy, Spain, Ireland, Belgium, and Greece) and Brazil. All episodes of candidemia and IAC in cirrhotic adult patients (>18 years) between January 2011 and December 2013 were included. Only the first episode for each patient was analyzed. Patient baseline characteristics and infection-related variables were collected from the hospital medical records, microbiology database, and pharmacy database of the participating centers. The institutional review board of the coordinating center (Udine) approved the study and because of its retrospective nature, the requirement for informed consent was waived.

Baseline characteristics included age, gender, comorbidities, Charlson comorbidity index [7], etiology of liver disease, Sequential Organ Failure Assessment (SOFA) score, and need for intensive care unit (ICU) admission. Infection characteristics examined were setting of acquisition, *Candida* species, type of invasive candidiasis (candidemia or abdominal candidiasis), prior abdominal surgery, vascular or abdominal device placement, prior antibiotic (more than 7 days in the previous 30 days) or azole exposure (in the previous 30 days), prior steroid treatment (prednisone 10 mg/day for 30 days or more) or immunosuppressive therapy.

Definitions

Cirrhosis was defined on the basis of histology or by clinical, analytical, and radiologic compatible findings [8]. Liver disease severity was assessed through Model for End-Stage Liver Disease (MELD) at diagnosis of candidemia or IAC [9]. Cirrhosis complications (ascites, encephalopathy, hepatorenal syndrome, and hepatocellular carcinoma) were defined according to European Association for the Study of the Liver (EASL) guidelines [10, 11].

Candidemia was defined as the isolation of *Candida* spp. from at least one blood culture, according to current guidelines [12, 13]. Episodes of IAC were defined as follows [14]: *Candida* detection by direct microscopy examination or growth in culture from purulent or necrotic intra-abdominal specimens obtained during surgery or by percutaneous aspiration; *Candida* growth from bile, intrabiliary duct devices, and biopsy of intra-abdominal organs; *Candida* growth from blood cultures in clinical setting of secondary and tertiary peritonitis; *Candida* growth from drainage tubes only if placed less than 24 h before the cultures.

Laboratory tests included median white blood cell (WBC) count, C-reactive protein (CRP, normal value <0.5 mg/dL), 1,3-β-D-glucan (BDG, normal value <80 pg/mL), and procalcitonin (PCT, normal value <0.15 ng/mL).

Infections were classified as community acquired (CA), health-care associated (HCA), and hospital acquired (HA) according to Friedman's criteria [15]. Septic shock was defined according to current sepsis guidelines [16]. Treatment-related characteristics included timing of adequate antifungal treatment in patients with blood or abdominal cultures positivity, type of antifungal used, and adequate source control. Antifungal therapy was considered adequate if the organism was shown to be susceptible to the prescribed antifungal treatment and the dosage of antifungal was adequate. The following antifungal dosages were considered adequate: (1) fluconazole 800 mg loading dose [for obese patients (BMI >30), 1200–1600 mg] followed by a daily dosage of at least 400 mg (600–800 mg for BMI >30); (2) liposomal amphotericin B (L-AmB) 3 mg/kg/day; (3) amphotericin lipid complex (ABLC) 5 mg/kg/day; (4) caspofungin 70 mg loading dose (100 mg for body weight >80 kg) followed by 50 mg/day (70 mg/day for body weight >80 kg); micafungin 100 mg/day; anidulafungin 200 mg loading dose followed by 100 mg/day. These dosages refer to patients with normal hepatic and renal function. In case of hepatic or renal impairment dose adjustments were

considered adequate according to the package indications. Source control measures were considered within the first 24–48 h from the determination of blood or abdominal culture positivity. Source control was considered adequate in the following cases: (1) removal of device or foreign bodies; (2) drainage of infected fluid collections; (3) debridement of infected solid tissue; (4) definitive measures to correct anatomic derangements resulting in microbial contamination. De-escalation of antifungal treatment was defined if the switch to a narrower spectrum agent and/or the interruption of the combination therapy and/or the administration of an oral treatment occurred [17]. Primary outcome was all-cause 30-day mortality.

Blood cultures and microbiology analysis

During the study period there were no changes in microbiological laboratory techniques among the 14 hospitals. *Candida* species were isolated using the BACTEC 860 system (Becton–Dickinson, Inc., Sparks, MD) and BacT/Alert 3D (bioMerieux). The species were identified using an API ID 32C system (bioMerieux, Marcy l'Etoile, France) or Vitek 2 system (bioMerieux). In the case of inconclusive results by both systems, isolates were identified using supplemental tests, e.g., presence or absence of well-formed pseudohyphae on cornmeal–Tween 80 agar and growth at 42–45 °C. This test was also required to differentiate isolates of *C. albicans* from those of *C. dubliniensis*. Antifungal susceptibility testing to amphotericin B, caspofungin, anidulafungin, micafungin, fluconazole, itraconazole, and voriconazole was performed using the Sensititre YeastOne colorimetric plate (Trek Diagnostics Systems, Cleveland, OH) or by agar diffusion, using E test strips (BioMerieux, France) and interpreted by the Clinical and Laboratory Standards Institute (CLSI) breakpoints.

Statistical analysis

Continuous and categorical data were reported as mean and standard deviation (SD) or median, 25th and 75th percentile, and frequency distributions, respectively. Differences in continuous variables between groups were evaluated through the Student *t* test or, when appropriate, the median test. Categorical variables were evaluated using Chi square or, when appropriate, the two-tailed Fisher's exact test. Given the multiple comparison at univariate analysis, the false discovery rate (FDR) estimates were computed from *P* values using the Benjamini and Hochberg procedure [18, 19] and reported in the tables. Multiple logistic regression analysis was performed to identify risk factors that were associated with septic shock and 30-day hospital mortality. Covariates that had a *P* value less than 0.10 after FDR computation in the univariate analysis and therapy-related variables were further evaluated for inclusion in multivariable regression models, using a backward stepwise algorithm. We evaluated collinearity between significant variables at univariate analysis cross-tabulating all combination of independent variables and examining the relationships between independent variables through Chi square or, when appropriate, the two-tailed Fisher's exact test (in the case of two categorical variables) and through the Student *t* test or, when appropriate, the median test (in the case of one categorical variable and one continuous variable). In the case of two continuous variables their collinearity was assessed by evaluating their correlation.

A backward stepwise algorithm was used to identify the best-fitting subset of variables for use in the final multivariable regression model. In particular, Akaike's information criterion (AIC) was used to assess the models' fit, and the model with the lowest AIC was selected for the multivariable analysis. Odds ratio (OR) and 95% confidence interval (95% CI) were reported. Moreover, we reported the AIC as a measure of the goodness of fit of each regression model and the area under the receiver operating characteristic (AUC) curve as an estimate of its predictive accuracy.

All tests were two-tailed, and a *P* value less than 0.05 was determined to represent statistical significance.

All statistical analyses were performed using JMP version 10.0 (SAS, NC, USA) and R version 3.3.2 (R Development Core Team).

Results

Population characteristics

A total of 241 patients affected by liver cirrhosis with candidemia and IAC were included in the study. Table 1 summarizes the characteristics of the study population. *Candida* spp. infections were classified as HA in the large majority of cases (86.3%) with a median time of 15 days (IQR 7–29) after hospital admission. At the time of diagnosis, most patients (121, 50.2%) were hospitalized in ICU and 68 (28.2%) in a medical ward. About 48% (116/241) of patients had been submitted to previous abdominal surgery.

The most common cause of liver disease was viral (41.1%) followed by alcohol abuse (40.7%). MELD score was between 15 and 25 in the majority of cases (41.5%) and was higher than 25 in 62 patients (25.7%) (Table 1). A high proportion of patients had more than one risk factor predisposing them to invasive candidiasis (IC) (Table 1).

Clinical presentation and septic shock

Candidemia accounted for 169 episodes (70.1%). IAC (72, 29.9%) consisted in peritonitis in the majority of cases (46, 63.9%), including spontaneous

Table 1 Demographic variables, setting of acquisition, baseline underlying condition, and clinical presentation of cirrhotic patients with candidemia and IAC

	Total $N = 241$	Survivors $N = 156$	Non-survivors $N = 85$	*P* values*
Baseline characteristics				
Age, years (median, IQR)	62 (51–71)	61 (50–70)	64 (52–71)	0.33
Sex, male *N* (%)	159 (66)	101 (64.7)	58 (68.2)	0.65
Setting of acquisition				
Hospital acquired	208 (86.3)	131 (84)	77 (90.6)	0.25
Health-care associated	18 (7.5)	12 (7.7)	6 (7.1)	0.88
Community acquired	15 (6.2)	13 (8.3)	2 (2.3)	0.17
Ward				
ICU	121 (50.2)	76 (48.7)	45 (52.9)	0.6
Internal medicine	68 (28.2)	40 (25.6)	28 (32.9)	0.33
Surgical ward	39 (16.2)	30 (19.2)	9 (10.6)	0.18
Other	13 (5.4)	10 (6.4)	3 (3.5)	0.6
Charlson score (median, IQR)	4 (2–6)	3 (2–6)	5 (3–7)	<0.001
SOFA score (median, IQR)	5 (3–9)	4 (3–6)	7 (5–1)	<0.001
Etiology of liver disease				
Viral (HBV and HCV)	99 (41.1)	60 (38.5)	39 (45.9)	0.36
Alcohol	98 (40.7)	58 (37.2)	40 (47.1)	0.24
Autoimmune	16 (6.6)	13 (8.3)	3 (3.5)	0.25
NAFDL	12 (5)	10 (6.4)	2 (2.4)	0.37
Cryptogenetic	16 (6.6)	15 (9.6)	1 (1.2)	0.04
MELD				
<15	79 (32.8)	72 (46.2)	7 (8.2)	<0.001
15–25	100 (41.5)	62 (39.7)	38 (44.7)	0.36
>25	62 (25.7)	22 (14.1)	40 (47.1)	<0.001
Comorbidities				
Diabetes	57 (23.7)	32 (20.5)	25 (29.4)	0.22
Heart disease	71 (29.5)	39 (25)	32 (37.7)	0.12
Renal failure (GFR <60 mL/min)	107 (44.4)	49 (31.4)	58 (68.2)	<0.001
Dialytic renal failure	51 (21.1)	29 (18.6)	22 (25.9)	0.3
Solid tumor	70 (29)	46 (29.5)	24 (28.2)	0.87
COPD	42 (17.4)	22 (14.1)	20 (23.5)	0.17
HIV infection	11 (4.6)	6 (3.9)	5 (5.9)	0.57
Liver transplant recipients	19 (7.9)	14 (9)	5 (5.9)	0.5
Hematologic malignancy	6 (2.5)	2 (1.3)	4 (4.7)	0.33
HCC	38 (15.8)	20 (12.8)	18 (21.2)	0.19
Previous abdominal surgery	116 (48.1)	87 (55.8)	29 (85)	0.005
Re-operation ($N = 116$)	47 (40.5)	39 (44.8)	8 (27.6)	0.2
Anastomotic leakage ($N = 116$)[a]	11 (9.5)	9 (10.3)	2 (6.9)	0.91
Vascular devices	154 (63.9)	87 (55.8)	67 (78.8)	<0.001
Abdominal devices	88 (36.5)	62 (39.7)	26 (30.6)	0.26
Parenteral nutrition	131 (54.4)	78 (50)	53 (62.4)	0.17
Recent antimicrobial therapy	203 (84.2)	122 (78.2)	81 (95.3)	<0.001
Steroid treatment	44 (18.3)	22 (14.1)	22 (25.9)	0.07
Immunosuppressants	31 (12.9)	23 (14.7)	8 (9.4)	0.34
Candida colonization	113 (46.9)	78 (50)	35 (41.2)	0.3
Candidemia	169 (70.1)	101 (64.7)	68 (80.0)	0.05
Abdominal candidiasis	72 (29.9)	55 (35.3)	17 (20.0)	0.05
Clinical presentation				
Fever ($T \geq 38$ °C)	146 (60.6)	93 (59.6)	53 (62.4)	0.74
Recent GI bleeding (1 month)	45 (18.7)	22 (14.1)	23 (27.1)	0.04
Ascites	155 (64.3)	96 (61.5)	59 (69.4)	0.33
Encephalopathy	84 (34.9)	38 (24.4)	46 (54.1)	<0.001
Concomitant bacterial infection	122 (50.6)	76 (48.6)	46 (54.1)	0.53
Septic shock	84 (34.9)	43 (27.6)	41 (48.2)	<0.001
ICU admission <72 h	106 (44)	71 (45.5)	35 (41.2)	0.6

HBV hepatitis B virus, *HCV* hepatitis C virus, *GFR* glomerular filtration rate, *GI* gastrointestinal, *HCC* hepatocellular carcinoma, *ICU* intensive care unit, *IQR* interquartile range, *MELD* Model for End-Stage Liver Disease, *NAFDL* non-alcoholic fatty liver disease, SOFA Sequential Organ Failure Assessment score

* *P* values adjusted using false discovery rate (FDR) method

[a] Anastomotic leakage includes biliary, gastric, or intestinal leakage

primary peritonitis (11/46, 15.3%) followed by abdominal abscesses (9, 12.5%). Biliary tract infections (7, 9.7%), pancreatitis (2, 2.8%), and other infection sites (8, 11.1%) were less common. Blood culture positivity was reported in only 12.5% of patients with IAC. Other sites of *Candida* isolation for patients with IAC were surgical or biliary drainage within 24 h after placement (25, 34.7%), ascitic fluid (24, 33.3%), and others (25, 34.7%).

At clinical presentation, only 60.6% ($N = 146$) presented with fever, 34.9% ($N = 84$) with encephalopathy, and 18.7% ($N = 45$) with gastrointestinal bleeding (Table 1).

A total of 84 patients (34.9%) developed septic shock and 106 (44%) were admitted to the ICUs ≤72 h after the onset of infection (Table 1). Table A (electronic supplemental material) summarizes the significant differences between patients with septic shock compared with patients without septic shock by univariate analysis.

Multivariable logistic regression analysis demonstrated that MELD score >25 (OR 2.4, 95% 1.5–4.3) and previous GI surgery (OR 0.2, 95% 0.1–1) were independent predictors of septic shock in patients with IC.

Table 2 summarizes the significant differences between patients admitted in the ICU ward compared with patients admitted in non-ICU wards by univariate analysis.

Table 3 summarizes the significant differences between patients with candidemia compared with patients with IAC by univariate analysis.

Candida species distribution and antifungal resistance

Candida albicans was the most common species and was isolated in 131 (54.4%) patients. Among non-albicans species, *C. glabrata* was the most frequently isolated (35, 14.5%), followed by *C. parapsilosis* (34, 14.1%) and *C. tropicalis* (14, 5.8%). A total of 20 (8.3%) patients had mixed *Candida* spp. infection and 122 (50.6%) had a concomitant bacterial infection. Distribution of *Candida* spp. in different clinical settings is listed in Table 4. Susceptibility tests showed significant levels of azole resistance (15.8% to fluconazole, 7.9% to voriconazole) and low levels of amphotericin B (4.9%) and caspofungin (3.4%) resistance.

Antifungal treatment and source control

Eighty-eight percent (213/241) of the patients received initial systemic antifungal therapy. Echinocandins were the most common antifungals used as initial treatment (44.8%), followed by azoles (34%) and amphotericin B (9.5%). Overall, 202 (83.8%) patients received an adequate definitive antibiotic therapy, in the majority of cases within 24 h after blood or abdominal culture positivity (60.6%) (Table 5). Adequate source control was performed in about half of patients ($n = 114$, 47.3%), in the majority of cases (60.5%) within 24 h after culture positivity. De-escalation therapy to fluconazole (in susceptible strains) was performed in only 20.4% of patients (38/186) after a median time of 5 days of treatment (IQR 3–10) (Table 5).

Outcome and risk factors for mortality

Of the 241 patients, 85 (35.3%) died within 30 days from the onset of IC. Tables 1, 3, and 4 summarize the significant differences between patients who died within 30 days from the diagnosis of *Candida* spp. infection compared with survivors by univariate analysis. Multivariable logistic regression analysis (Table 6) demonstrated that candidemia (OR 2.2, 95% CI 1.2–4.5) and septic shock (OR 3.2, 95% CI 1.7–6) were independent predictors of 30 days mortality in patients with IC (Table 5). Adequate antifungal treatment (OR 0.4, 95% CI 0.3–0.9) was associated with a decreased risk of 30-day mortality (OR 0.3).

Discussion

To the best of our knowledge, is the first large multicenter study describing the epidemiology and prognostic factors for mortality in cirrhotic patients with candidemia and IAC.

In our study, IC was mainly hospital acquired, frequent in ICU, and occurred late after admission. Previous studies on critically ill cirrhotic patients showed higher prevalence of *Candida* infections compared to other patient populations [20–22]. Risk factors for candidemia among cirrhotic patients include ICU admission that can favor *Candida* colonization along with parenteral nutrition, vascular and abdominal devices, abdominal surgery, and recent antimicrobial therapy [23]. Furthermore, 20% of patients had a recent history of gastrointestinal bleeding, which is a known predisposing factor for bacterial infections [24]. In our study, clinical presentation of IC was often atypical, including absence of fever in up to 40% of patients (mostly IAC) and common presentation with new onset of hepatic encephalopathy. An increased risk of IC in cirrhotic patients, however, is still debated, and delayed diagnosis due to low index of suspicion is common [3].

In our study, one quarter of patients presented with primary fungal peritonitis, which has been previously associated with nosocomial setting, high Child–Pugh score, and significant worse prognosis compared to bacterial peritonitis [3, 6]. *Candida* detection from ascites should therefore always be considered in cirrhotic patients presenting with nosocomial infections. Overall, the diagnosis of IAC remains a major challenge because of the low sensitivity and a delayed time to positivity of cultures [14]. Similar to other reports, candidemia was reported only in 12.5% of patients with IAC in our study [40]. Blood cultures remain a key diagnostic tool, but should not replace surgical or abdominal cultures in patients at high risk for IAC [14]. In this setting, non-cultural tests such as BDG could be useful to support the diagnosis of IC [25, 26].

Concomitant bacterial infections are present in up to one-third of IC, may modulate the virulence of *Candida* spp., and are associated with high mortality [27–29]. Although a high percentage of patients with IAC had bacterial infections, there was not an association between concomitant *Candida* and bacterial infections and mortality.

Previous studies reported 30-day crude mortality rates in cirrhotic patients with *Candida* infections up to 56% [5, 30]. In our report, mortality rates were lower

Table 2 Differences between patients hospitalized in ICU ward compared with patients hospitalized in other wards at the time of candidiasis diagnosis

	Total $N = 241$	ICU ward $N = 121$	Non-ICU ward $N = 120$	*P* values*
SOFA score (median, IQR)	5 (3–9)	8 (5–11.5)	4 (3–7)	0.02
MELD				
<15	79 (32.8)	24 (19.8)	55 (45.8)	0.002
15–25	100 (41.5)	56 (46.3)	44 (36.7)	0.23
>25	62 (25.7)	41 (33.9)	21 (17.5)	0.02
Dialytic renal failure	51 (21.1)	43 (35.5)	8 (6.7)	0.002
Candida colonization	113 (46.9)	81 (66.9)	32 (26.7)	0.002
Clinical presentation				
Acute on chronic liver failure	108 (44.8)	54 (44.6)	54 (45.0)	0.002
Fever ($T \geq 38$ °C)	146 (60.6)	65 (53.7)	81 (67.5)	0.08
Recent GI bleeding (1 month)	45 (18.7)	26 (21.5)	19 (15.8)	0.03
Ascites	155 (64.3)	58 (47.9)	97 (80.8)	0.002
Concomitant bacterial infection	122 (50.6)	75 (62.0)	47 (39.2)	0.004
Septic shock	84 (34.9)	63 (52.1)	21 (17.5)	0.002
Timing of adequate source control ($N = 114$)				
Within 24 h	69 (60.5)	48 (73.8)	21 (42.9)	0.008
24–48 h	27 (23.7)	14 (215)	13 (26.5)	0.62
48–72 h	9 (7.9)	1 (1.5)	8 (16.3)	0.02
>72	9 (7.9)	2 (3.1)	7 (14.3)	0.1
Initial antifungal treatment				
Amphotericin B	23 (9.5)	20 (16.5)	3 (2.5)	0.002
Azoles	82 (34.0)	30 (24.8)	52 (43.3)	0.02
Echinocandin	108 (44.8)	62 (51.2)	46 (38.3)	0.1
None	28 (11.6)	9 (7.4)	19 (15.8)	0.1
Adequate antifungal treatment (according to susceptibility test and dose)	202 (83.8)	108 (89.3)	94 (78.3)	0.06
Duration of antifungal treatment (days) (median, IQR)	14 (6–21)	14 (10–25)	11.5 (4–19)	0.01
De-escalation to fluconazole (if susceptible strain) ($N = 186$)	38 (20.4)	14 (13.5)	24 (29.3)	0.03

HBV hepatitis B virus, *HCV* hepatitis C virus, *GFR* glomerular filtration rate, *GI* gastrointestinal, *HCC* hepatocellular carcinoma, *ICU* intensive care unit, *IQR* interquartile range, *MELD* Model for End-Stage Liver Disease, *NAFDL* non-alcoholic fatty liver disease, *SOFA* Sequential Organ Failure Assessment score

* *P* values adjusted using false discovery rate (FDR) method

compared to other studies and were increased in candidemia compared to IAC [31–33].

Specific scores are associated with mortality in patients with advanced liver disease with infections [34, 35]. In our cohort, the majority of patients presented with decompensated cirrhosis [1], emphasizing the need for guidelines addressing the management of invasive fungal infections (IFI) in end-stage liver patients [36]. No prophylactic strategy, however, can be recommended in this population on the basis of currently available data. In our cohort high MELD score (>25) was an independent predictor of septic shock in patients with IC. Cirrhosis and portal hypertension also induce immunological impairment and adrenal insufficiency, leading to organ failure [1, 37]. In our study 40% of patients developed septic shock compared to 20% in previous studies [32, 38].

In patients with IC the association of a timely adequate treatment with source control is crucial for survival [32, 39, 40]. In our study both source control and adequate antifungal therapy were achieved in a high proportion of patients. Adequate antifungal therapy was associated with survival, although the effect of antifungal administration timing on mortality was not confirmed [41, 42].

The selection of the antifungal regimen in treating IC should take into consideration the knowledge of local epidemiological data. Increased rates of non-albicans isolates in critically ill patients with IAC [31] or candidemia [43–45] have been reported. In our study, *C. albicans* accounted for half of the isolates, confirming a trend towards increasing prevalence of non-albicans species in patients with advanced liver disease. Lower mortality rates were associated with *C. parapsilosis* candidemia while higher rates were associated with *C. tropicalis*. Up

Table 3 Differences between patients with candidemia compared with patients with IAC by univariate analysis

	Total *N* = 241	Candidemia *N* = 169	IAC *N* = 72	*P* value
Ward				
ICU	121 (50.2)	79 (46.7)	42 (58.3)	0.1
Internal medicine	68 (28.2)	63 (37.3)	5 (7)	<0.001
Surgical ward	39 (16.2)	21 (12.4)	18 (25)	0.02
Other	13 (5.4)	6 (3.6)	7 (9.7)	0.11
SOFA score (median, IQR)	5 (3–9)	6 (4–10)	4 (2–6)	0.004
Charlson score (median, IQR)	4 (2–6)	4 (3–6.5)	3 (2–5)	0.02
MELD				
<15	79 (32.8)	48 (28.4)	31 (43.1)	0.03
15–25	100 (41.5)	71 (42)	29 (40.3)	0.8
>25	62 (25.8)	50 (29.6)	12 (16.7)	0.04
HCC	38 (15.8)	18 (10.7)	20 (27.8)	<0.001
Previous abdominal surgery	116 (48.1)	59 (34.9)	57 (79.2)	<0.001
Re-operation (*N* = 116)	47 (40.5)	15 (25.4)	32 (56.1)	<0.001
Vascular devices	154 (63.9)	126 (74.6)	28 (38.9)	<0.001
Abdominal devices	88 (36.5)	37 (21.9)	51 (70.8)	<0.001
Recent antimicrobial therapy	203 (84.2)	148 (87.6)	55 (76.4)	0.03
Fever (*T* ≥38 °C)	146 (60.6)	115 (68.1)	31 (43.1)	<0.001
Concomitant bacterial infection	122 (50.6)	74 (43.8)	48 (66.7)	0.001
ICU admission <72 h	106 (44)	63 (37.3)	43 (62.3)	0.001
Laboratory findings				
Fluconazole-S (*N* = 240)	202 (84.2)	148 (88.1)	54 (75)	0.01
Timing of adequate antifungal treatment (*N* = 188)				
Within 24 h	114 (60.7)	72 (52.9)	42 (80.8)	<0.001
24–48 h	32 (17)	29 (21.3)	3 (5.8)	0.01
48–72 h	19 (10.1)	18 (13.2)	1 (1.9)	0.02
>72 h	23 (12.2)	17 (12.5)	6 (11.5)	0.86
Death within 30 days	85 (35.3)	68 (40.2)	17 (23.6)	0.01

HBV hepatitis B virus, *HCV* hepatitis C virus, *ICU* intensive care unit, *IQR* interquartile range, *NAFDL* non-alcoholic fatty liver disease, *GFR* glomerular filtration rate *GI* gastrointestinal, *HCC* hepatocellular carcinoma, *MELD* Model for End-Stage Liver Disease

Table 4 Candida species distribution and antifungal resistance in cirrhotic patients with candidemia and IAC

	Total *N* = 241	Survivors *N* = 156	Non-survivors *N* = 85	*P* values*
Candida species				
C. albicans	131 (54.4)	79 (50.6)	52 (61.2)	0.22
C. glabrata	35 (14.5)	27 (17.3)	8 (9.4)	0.2
C. parapsilosis	34 (14.1)	27 (17.3)	7 (8.2)	0.14
C. tropicalis	14 (5.8)	6 (3.9)	8 (9.4)	0.18
C. kruzei	6 (2.5)	6 (3.9)	0	0.24
C. dubliniensis	1 (0.4)	0	1 (1.2)	0.77
More than 1 *Candida*	20 (8.3)	11 (7.1)	9 (10.6)	0.44
Fluconazole-S (*N* = 240)	202 (84.2)	133 (85.3)	69 (82.1)	0.6
Caspofungin-S (*N* = 240)	233 (97.1)	154 (98.7)	79 (94.1)	0.12
Voriconazole-S (*N* = 240)	221 (92.1)	147 (94.2)	74 (88.1)	0.19
Amphotericin B-S (*N* = 222)	212 (95.5)	137 (95.8)	75 (94.9)	0.82

* *P* values adjusted using false discovery rate (FDR) method

to 15% of patients had previous exposure to azole therapy; about 16% of *Candida* isolates were resistant to fluconazole. We did not observe an impact of azole susceptibility on patient mortality.

In contrast with previous reports [31, 32], echinocandins were the most commonly used antifungals. We attributed the preference for echinocandin use to the high incidence of septic shock along with their overall low toxicity. Compared to fluconazole, in particular, echinocandins have shown high tolerability and low hepatotoxicity, even among patients with liver impairment [46–48]. As a result of their increased use, echinocandin resistance represents a concern in *Candida* infections [49]. Overall, resistance to echinocandins remained relatively low in our study but we believe that antifungal resistance needs to be monitored in cirrhotic patients with factors that may promote resistance to echinocandins (e.g., gastrointestinal tract reservoirs) [49]. De-escalation therapy to azoles should be encouraged in clinically stable patients. In our cohort, only 20% of patients switched from an echinocandin to fluconazole, as reported in other studies [50, 51]. Although de-escalation to fluconazole was associated with a survival benefit at univariate analysis, this data was probably related to patients' improvement. De-escalation therapy has also been recommended among non-neutropenic critically ill patients with IC [51].

Our study has some limitations, such as its observational nature and a potential bias in data collection including source control and adequate therapy timing, which may have varied from one site to another. The patient population was heterogeneous and presented multiple factors for immune depression (e.g., malignancy, transplant, renal impairment, alcohol abuse, etc.) and concomitant bacterial infections that may have had an impact on the outcome. Cirrhotics, however, usually have multiple comorbidities that can favor fungal infection. Furthermore, we considered overall in-hospital mortality rather than IC-related mortality. However, our methodological strategy was preferred to the bias created by a retrospective review of causes of death. Finally, baseline status and co-morbidities of cirrhotic patients may

Table 5 Antifungal treatment and source control of cirrhotic patients with candidemia and IAC

	Total $N = 241$	Survivors $N = 156$	Non-survivors $N = 85$	*P* values*
Adequate source control	114 (47.3)	81 (51.9)	33 (38.8)	0.14
Timing of adequate source control ($N = 114$)				
Within 24 h	69 (60.5)	50 (61.7)	19 (57.6)	0.74
24–48 h	27 (23.7)	16 (19.8)	11 (33.3)	0.22
48–72 h	9 (7.9)	9 (11.1)	0 (0)	0.18
>72 h	9 (7.9)	6 (7.4)	3 (9.1)	>0.99
Initial antifungal treatment				
Echinocandins	108 (44.8)	80 (51.3)	28 (32.9)	0.03
Azoles	82 (34)	54 (34.6)	28 (32.9)	0.83
Amphotericin B	23 (9.5)	11 (7.1)	12 (14.1)	0.17
None	28 (11.6)	11 (7.1)	17 (20)	0.01
Adequate antifungal treatment	202 (83.8)	138 (88.5)	64 (75.3)	0.03
Timing of adequate antifungal treatment ($N = 188$)				
Within 24 h	114 (60.6)	80/128 (62.6)	34/60 (56.7)	0.56
24–48 h	32 (17)	19/128 (14.8)	13/60 (21.7)	0.35
48–72 h	19 (10.1)	10/128 (7.8)	9/60 (15)	0.23
>72 h	23 (12.2)	19/128 (14.8)	4/60 (6.6)	0.22
Duration of antifungal treatment (days) (median, IQR)	14 (6–21)	16 (13–28)	6 (1.5–14)	<0.001
De-escalation to fluconazole ($N = 186$)	38 (20.4)	32/123 (26)	6/63 (9.5)	0.03
Timing (days) of de-escalation to fluconazole (median, IQR)	5 (3–10)	5 (4–10)	3.5 (0–14.5)	0.57

* *P* values adjusted using false discovery rate (FDR) method

Table 6 Multivariate analysis of risk factors for mortality at 30 days from candidemia and IAC in cirrhotic patients (AIC 184.9, AUC 0.75)

Variables	X^2	OR (95% CI)	*P* value
Candidemia	5.5	2.2 (1.1–4.5)	0.02
Septic shock	13.9	3.2 (1.7–6)	<0.001
Adequate antifungal treatment	5.1	0.4 (0.2–0.9)	0.02

MELD, acute on chronic liver failure, encephalopathy, Charlson score, SOFA, renal failure (GFR <60 mL/min), previous abdominal surgery, abdominal candidiasis, recent antimicrobial therapy, steroid treatment, recent GI bleeding, no initial antifungal treatment, and echinocandin antifungal treatment were excluded for collinearity. Duration of antifungal treatment was excluded because it was influenced by mortality

The following variables were included in the backward stepwise algorithm: cryptogenic etiology of liver disease, vascular device, candidemia, hepatorenal syndrome, septic shock, adequate antifungal treatment, de-escalation to fluconazole

AIC Akaike's information criterion, *AUC* area under the receiver operating characteristic curve

have affected clinical management thereby impacting the overall mortality.

In conclusion, our study identified relevant characteristics and determinants of mortality in patients with end-stage liver disease and *Candida* infections. We confirmed a shift toward an increasing prevalence of *C. glabrata* and *C. parapsilosis* species in patients with liver disease. Candidemia and IAC were associated with significant mortality in cirrhotic patients. Mortality was associated with candidemia and septic shock, while adequate antifungal treatment was associated with survival in cirrhotic patients. Physicians should be aware of the threat of fungal infections in patients with advanced liver disease and severe clinical presentations in order to administer prompt adequate antifungal treatment. Future studies investigating the risk of *Candida* infections according to the severity of cirrhosis and monitoring epidemiological shifts and resistance patterns of *Candida* species in cohort are largely awaited.

Abbreviations

CA: Community associated; CAID: Cirrhosis-associated immune dysfunction; CVC: Central venous catheter; IAC: Intra-abdominal candidiasis; ICU: Intensive care unit; IFI: Invasive fungal infections; MELD: Model for End-Stage Liver Disease; OR: Odds ratio.

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Compliance with ethical standards

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