Invasive Fungal Infections Are Underdiagnosed in Hospitalized Patients With Decompensated Cirrhosis: An Autopsy Study

Patients with decompensated cirrhosis have an increased risk for developing invasive fungal infections. Among those in the intensive care unit or with acute-on-chronic liver failure (ACLF), the prevalence ranges from 10% to 15%.\(^1\) *Candida* and *Aspergillus* species predominate, and the most common sites of infection are the lungs, urinary tract, and bloodstream. Risk factors include markers of advanced cirrhosis, antibiotic or steroid use, indwelling catheters, gastrointestinal endoscopy, and additional immunocompromising conditions.\(^2\)\(^-\)\(^4\)

Invasive fungal infections portend dismal prognoses in patients with cirrhosis with mortality rates in excess of 50% for invasive candidiasis and 80% for invasive aspergillosis.\(^5\)\(^,\)\(^6\) This is partially because of factors that are not readily modifiable, including impaired host immunity and increasing rates of drug resistance.\(^7\)

However, delays in diagnosis also contribute to poor clinical outcomes, and this continues to be a common problem despite the emergence of sensitive diagnostic tools such as 1,3-β-D-glucan and galactomannan assays.\(^3\)\(^,\)\(^8\)\(^,\)\(^9\)

The aim of this study was to evaluate our ability to diagnose fungal infections in patients with decompensated cirrhosis. In contrast to prior studies, which characterized such infections using clinical tools only, we obtained autopsy records and compared premortem serologic and culture data to postmortem histopathology and culture data from deceased patients.

Institutional review board determination was waived by Yale-New Haven Hospital because the study only included deceased patients, and privacy was ensured. Electronic pathology records were initially screened for those with cirrhosis who underwent autopsies between 2012 and 2022. Corresponding electronic medical records were subsequently reviewed. Patients were excluded if they did not have decompensated cirrhosis, had insufficient clinical data, underwent organ donation, or had autopsies that did not include examination of both the chest and abdomen. Baseline clinical data, including demographics, medical history, liver disease etiology, liver-related complications, medication use, and laboratory results, were captured at the time of admission, and Child-Turcotte-Pugh and model for end-stage liver disease-sodium scores were calculated. Microbiology results (cultures and serologic assays), management details (use of antimicrobial agents, steroids, and mechanical support), and cause of death were collected during the hospitalization and/or at the time of death. Autopsy records were then reviewed to determine whether invasive fungal infections were present in any organs, including the bloodstream. Fungal organisms were identified on histopathology using Grocott methenamine silver and periodic acid-Schiff stains.

For the purposes of this study, some autopsy specimens were re-evaluated for clarification when deemed necessary. Over a period of 10 years, 142 patients were screened using the pathology database, and 96 were included in our study (Table 1). The most common reason for exclusion was lack of decompensated cirrhosis (24 patients). The median age of our study cohort was 60 years (interquartile range 12); 44 (46%) were women and 40 (42%) had cirrhosis related to alcohol use alone or in combination with chronic hepatitis C virus infection. The median model for end-stage liver disease-sodium was 25 (interquartile range 13); 86 (90%) were classified as Child-Turcotte-Pugh C and 82 (85%) had ascites. The most common comorbidities were diabetes mellitus, cardiovascular disease, and chronic kidney disease, whereas human immunodeficiency virus infection and metastatic cancer were rare. Critical illness was common: 81 patients (84%) developed shock requiring vasopressors and 82 (85%) developed respiratory failure requiring mechanical ventilation. Antimicrobial use was nearly ubiquitous, given the high frequency of sepsis, and steroid use was also common, often used in high doses for refractory septic shock.

In total, 17 patients (18%) had invasive fungal infections on autopsy, of which 11 had *Candida*, 4 had both *Candida* and *Aspergillus*, and 2 had *Cryptococcus* (Table 2). Most patients had disseminated infections, and the most common organ affected was the lung (13 patients). Only 7 patients with invasive fungal infections had one or more premortem serum-based serologic assays performed, including 3 who had 1,3-β-D-glucan assays (all positive). Importantly, of those with invasive fungal infections on autopsy, 6 (35%) were not diagnosed clinically before death, although 4 of them received empiric antifungal therapy. All 6 patients had *Candida* infections; only one underwent 1,3-β-D-glucan testing, which returned positive after death. Of the 79 patients without invasive fungal infections on autopsy, 7 had positive premortem urine, respiratory, or peritoneal fluid cultures or esophageal biopsies positive for *Candida* at some point during their hospitalization.

Our study suggests that invasive fungal infections are common among patients with decompensated cirrhosis who undergo autopsy but are clinically underdiagnosed before death, often due to a lack of sufficient and timely testing. Although most patients with fungal infections in our cohort received...
empiric antifungal therapy, this observation does not negate the need to isolate pathogenic organisms due to factors such as drug resistance. However, our findings must be interpreted cautiously in the context of our study design and its inherent limitations. As a consequence of only including patients who underwent autopsy, the prevalence of invasive fungal infections described in our study may be higher than the prevalence among

Table 1. Patient Characteristics

| Patient factors                  | Invasive fungal infections (n = 17) | No invasive fungal infections (n = 79) | Entire cohort (n = 96) |
|----------------------------------|------------------------------------|--------------------------------------|-----------------------|
| Demographics                     | n % Median IQR                      | n % Median IQR                        | n % Median IQR        |
| Age                              | 54 17                               | 60 12                                | 60 12                 |
| Sex (female)                     | 10 59                               | 34 43                                | 44 46                 |
| Race (White)                     | 12 71                               | 44 56                                | 56 58                 |
| Cirrhosis-related factors        |                                    |                                     |                       |
| Etiology (alcohol related)       | 8 47                                | 32 41                                | 40 42                 |
| MELD-Na                          | 24 14                               | 25 14                                | 25 13                 |
| CTP (class C)                    |                                     |                                     |                       |
| Ascites                          | 15 88                               | 67 85                                | 82 85                 |
| Hepatic encephalopathy          | 10 59                               | 44 56                                | 54 56                 |
| Variceal hemorrhage              | 2 12                                | 14 18                                | 16 17                 |
| Jaundice                         | 11 65                               | 43 54                                | 54 56                 |
| Hepatocellular carcinoma        | 1 6                                 | 7 9                                  | 8 8                   |
| Comorbidities                    |                                    |                                     |                       |
| Chronic obstructive pulmonary disease |                                   |                                     |                       |
| Chronic kidney disease           | 0 0                                 | 24 30                                | 24 25                 |
| Cardiovascular disease           | 2 12                                | 24 30                                | 26 27                 |
| HIV infection                    | 1 6                                 | 4 5                                  | 5 5                   |
| Diabetes mellitus                | 4 24                                | 27 34                                | 31 32                 |
| Metastatic cancer                | 1 6                                 | 8 10                                 | 9 9                   |
| Laboratory parameters            |                                    |                                     |                       |
| Sodium (mEq/L)                   | 135 5                               | 136 8                                | 136 7                 |
| Creatinine (mg/dL)               | 1.3 0.7                             | 1.4 1.8                              | 1.3 1.6               |
| ALT (U/L)                        | 47 36                               | 41 34                                | 41 40                 |
| AST (U/L)                        | 123 95                              | 91 110                               | 94 107                |
| Alkaline phosphatase (U/L)       | 162 116                             | 155 94                               | 158 95                |
| Total bilirubin (mg/dL)          | 4.5 8.9                             | 3.4 5.0                              | 3.5 6.0               |
| Albumin (g/dL)                   | 2.5 1.0                             | 2.6 0.9                              | 2.6 0.9               |
| WBC (10^9/L)                     | 11.5 8.4                            | 10.0 9.2                             | 10.2 9.6              |
| Hemoglobin (g/dL)                | 10.6 4.5                            | 10.5 3.6                             | 10.5 3.8              |
| Platelets (10^9/L)               | 120 106                             | 117 90                               | 120 99                |
| INR                              | 1.8 1.0                             | 1.6 0.5                              | 1.6 0.6               |
| Microbiology (positive bacterial cultures) |            |                                     |                       |
| Blood                            | 6 35                                | 20 25                                | 26 27                 |
| Urine                            | 5 29                                | 12 15                                | 17 18                 |
| Sputum                           | 4 24                                | 10 13                                | 14 15                 |
| Peritoneal fluid                 | 4 24                                | 8 10                                 | 12 13                 |
| Mechanical support               |                                    |                                     |                       |
| Vasopressors                     | 15 88                               | 66 84                                | 81 84                 |
| Mechanical ventilation           | 15 88                               | 67 85                                | 82 85                 |
| Dialysis                         | 8 47                                | 28 35                                | 36 38                 |
| Medications                      |                                    |                                     |                       |
| Antibiotics                      | 17 100                              | 75 95                                | 92 96                 |
| Antifungals                      | 15 88                               | 17 22                                | 32 33                 |
| Systemic steroids                | 13 76                               | 49 62                                | 62 65                 |
| Cause of death                   |                                    |                                     |                       |
| Sepsis (primary or contributing) | 17 100                              | 59 75                                | 76 79                 |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTP, Child-Turcotte-Pugh; FIB-4, Fibrosis-4; HIV, human immunodeficiency virus; INR, international normalized ratio; IQR, interquartile range; MELD-Na, model for end-stage liver disease-sodium; WBC, white blood cell count.

*4 cases were possible contaminants.
| Age | Sex | Cause of cirrhosis | MELD-Na | CTP | Comorbidities | Mechanical support | Premortem fungal cultures or pathology | Serum fungal markers | Antifungal therapy | Autopsy findings |
|-----|-----|-------------------|---------|-----|--------------|-------------------|---------------------|---------------------|-------------------|------------------|
| 46 F | HCV | 15 | C10 | HIV, DM | None | Cryptococcus (B) | Not done | Not done | Yes | Cryptococcus (disseminated) |
| 62 M | HCV | 17 | C11 | CVD | P, MV, RRT | Candida (B), Aspergillus (R) | Not done | Not done | Yes | Candida (disseminated) |
| 48 M | Alcohol | 18 | C10 | None | P, MV, RRT | Candida (U, pleural) | Not done | Not done | Yes | Candida (disseminated) |
| 61 F | Hemosiderosis | 19 | C11 | CVD, MDS | P, MV | Candida (U) | Not done | Not done | Yes | Candida (disseminated) |
| 68 F | Cryptogenic | 21 | C14 | DM | P, MV | Candida (U), Aspergillus (R) | Not done | Not done | Yes | Candida (stomach), Aspergillus (lung) |
| 32 M | Alcohol | 24 | C12 | None | P, MV, RRT | Candida (B, U) | Not done | Negative | Yes | Candida (lung) |
| 65 F | Cryptogenic | 24 | C13 | None | P, MV | Candida (U), Aspergillus (R) | Positive | Negative | Yes | Candida (disseminated), Aspergillus (lung) |
| 69 M | NASH | 28 | C14 | DM, HCC | P, MV | Cryptococcus (B, CSF) | Not done | Not done | Yes | Cryptococcus (CNS) |
| 65 M | Alcohol | 31 | C12 | DM | P, MV, RRT | Candida (U) | Not done | Not done | Yes | Candida (soft tissue) |
| 42 F | Alcohol | 35 | C11 | None | P, MV, RRT | Candida (U), Aspergillus (R) | Not done | Positive | Yes | Candida (intestine), Aspergillus (disseminated) |
| 51 M | Alcohol | 37 | C13 | None | P, MV | Candida (esophageal) | Positive | Not done | Yes | Candida and Aspergillus (both disseminated) |

Patients with invasive fungal infections not diagnosed before death

| Age | Sex | Cause of cirrhosis | MELD-Na | CTP | Comorbidities | Mechanical support | Premortem fungal cultures or pathology | Serum fungal markers | Antifungal therapy | Autopsy findings |
|-----|-----|-------------------|---------|-----|--------------|-------------------|---------------------|---------------------|-------------------|------------------|
| 54 F | AIH | 9 | C11 | Gastric cancer | P, MV | Negative | Not done | Not done | Yes | Candida (lung) |
| 67 F | NASH | 19 | B9 | None | P, MV, RRT | Negative | Positive | Negative | Yes | Candida (lung) |
| 54 F | Alcohol | 28 | C14 | None | P, MV, RRT | Negative | Not done | Not done | Yes | Candida (esophagus) |
| 52 F | Alcohol/HCV | 33 | C14 | None | P, MV | Candida (B) | Not done | Not done | No | Candida (disseminated) |
| 53 M | Alcohol | 37 | C13 | None | None | Negative | Not done | Not done | No | Candida (disseminated) |
| 44 F | Cryptogenic | 40 | C14 | None | P, MV, RRT | Negative | Not done | Not done | Yes | Candida (blood) |

1,3-β-D-Glucan; B, blood; CNS, central nervous system; CSF, cerebrospinal fluid; CTP, Child-Turcotte-Pugh; CVD, cardiovascular disease; DM, diabetes mellitus; F, female; GAL, galactomannan; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; M, male; MDS, myelodysplastic syndrome; MELD-Na, model for end-stage liver disease-sodium; MV, mechanical ventilation; NASH, non-alcoholic steatohepatitis; P, pressor; R, respiratory; RRT, renal replacement therapy; U, urine.

*Results of test became available after patient death.
all hospitalized patients with decompensated cirrhosis. In addition, our sample size limitations precluded meaningful statistical analysis relating to risk factors for fungal infections.

As most invasive fungal infections among patients with cirrhosis are due to Candida species and occur at a significantly higher rate among those in the intensive care unit or with ACLF, it would be prudent to perform early 1,3-β-D-glucan testing, in addition to standard cultures, among this high-risk subset. We believe that this should occur either at the time of hospitalization for those who present with critical illness or ACLF or at the time of further clinical decompensation for patients who are initially stable. Additional testing for galactomannan and Cryptococcus antigen can be considered on a case-by-case basis, including among those who cannot be weaned from mechanical support, receive immunosuppressive therapy, or have underlying impaired T-cell immunity, although further studies are necessary before formal recommendations can be implemented.

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Abbreviations used in this paper: ACLF, acute-on-chronic liver failure

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The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
Deidentified patient data may be made available upon request after review of submitted research proposals.