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

S. SAFFO, MD[1], **D. JAIN, MD**[2], **H. SANCHEZ, MD**[2], **G. GARCIA-TSAO, MD**[1,3]

[1]Section of Digestive Diseases, Yale School of Medicine, New Haven, Connecticut

[2]Department of Pathology, Yale School of Medicine, New Haven, Connecticut

[3]Section of Digestive Diseases, VA Connecticut Healthcare System, West Haven, Connecticut

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

Correspondence: Address correspondence to: Saad Saffo, MD, Section of Digestive Diseases, Yale University School of Medicine, 333 Cedar Street, 1080 LMP, New Haven, Connecticut 06520-8019. saad.saffo@yale.edu.

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The authors disclose no conflicts.

Ethical Statement:
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.

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 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.[10]

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Data Transparency Statement:

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

Abbreviations used in this paper:

ACLF	acute-on-chronic liver failure

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Table 1.

Patient Characteristics

	Invasive fungal infections (n = 17)				No invasive fungal infections (n = 79)				Entire cohort (n = 96)			
Patient factors	**n**	**%**	**Median**	**IQR**	**n**	**%**	**Median**	**IQR**	**n**	**%**	**Median**	**IQR**
Demographics												
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)	16	94			70	89			86	90		
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	0				14	18			14	15		
Chronic kidney disease	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

	Invasive fungal infections (n = 17)				No invasive fungal infections (n = 79)				Entire cohort (n = 96)			
Patient factors	**n**	**%**	**Median**	**IQR**	**n**	**%**	**Median**	**IQR**	**n**	**%**	**Median**	**IQR**
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 (109/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[a]	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.

[a] 4 cases were possible contaminants.

Table 2.

Clinical and Pathologic Findings in Patients With Invasive Fungal Infections

Age	Sex	Cause of cirrhosis	MELD-Na	CTP	Comorbidities	Mechanical support	Premortem fungal cultures or pathology	Serum fungal markers		Antifungal therapy	Autopsy findings
								1,3-βDG	GAL		
Patients with invasive fungal infections diagnosed before death											
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											
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[a]	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)[a]	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-βDG, 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.

[a]Results of test became available after patient death.