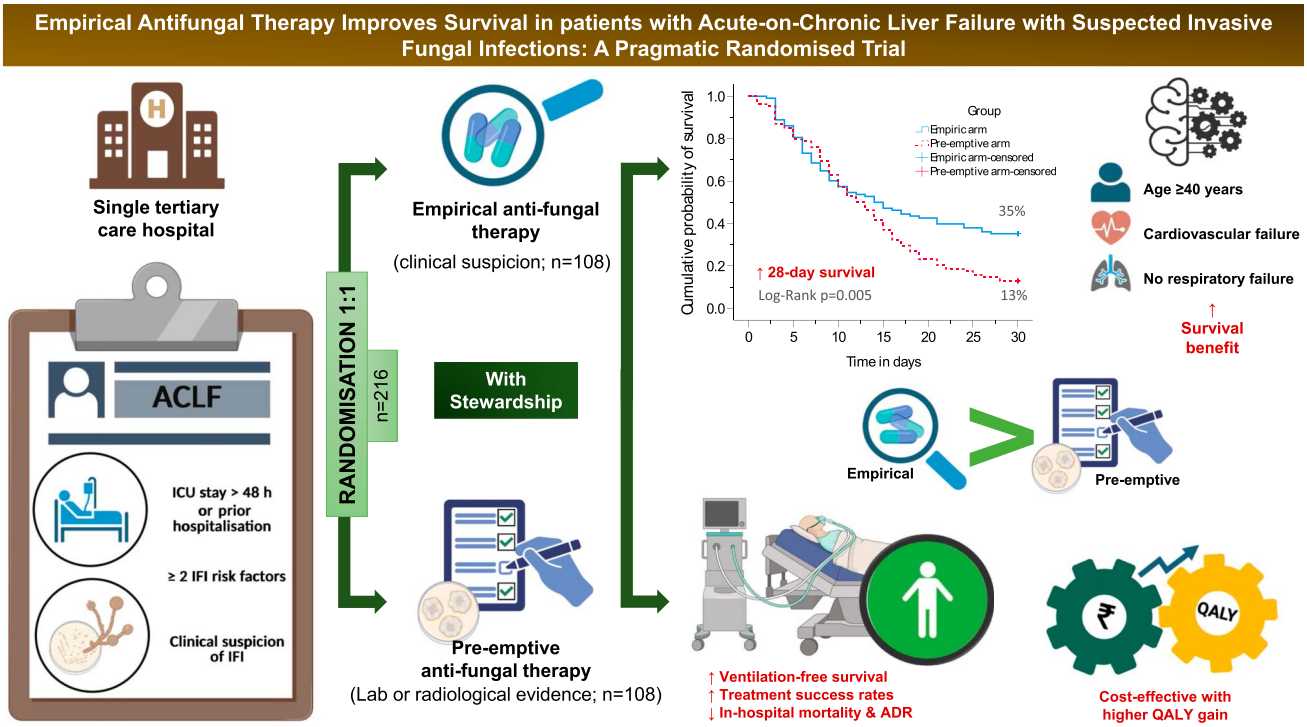
Empirical Antifungal Therapy Improves Survival in Patients With Acute-on-Chronic Liver Failure With Suspected Invasive Fungal Infections: A Pragmatic Randomized Trial

Nipun Verma, MD, DM[1,*†], Arun Valsan, MD, DM[2,*], Pratibha Garg, MSc[1], Shreeja Sarabu, MPH[3], Parminder Kaur, PhD[1], Nimitha Mohan, MD[4], Arka De, MD, DM[1], Madhumita Premkumar, MD, DM[1], Sunil Taneja, MD, DM[1], Shankar Prinja, MD[3], Arunaloke Chakrabarti, MD[5,†], Nusrat Shafiq, MD[6,†] and Ajay Duseja, MD, DM[1,†]

INTRODUCTION: **Invasive fungal infections (IFIs) in acute-on-chronic liver failure (ACLF) are associated with transplant delistings, high morbidity, and mortality. An optimal strategy of antifungal therapy in this setting remains uncertain. We compared suspicion-based (empirical) with investigation-driven (diagnostic/biomarker-driven-pre-emptive) antifungal therapy among patients with ACLF in a high-burden setting.**



doi: 10.14309/ajg.0000000000003832

[1]Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh; [2]Department of Hepatology, Amrita Institute of Medical Sciences, Kochi; [3]Department of Community Medicine and School of Public Health, Postgraduate Institute of Medical Education and Research, Chandigarh; [4]Department of Microbiology, Aster Medicity, Kochi; [5]Department of Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh; [6]Clinical Pharmacology Unit, Postgraduate Institute of Medical Education and Research, Chandigarh. **Correspondence:** Nipun Verma, MD, DM. E-mail: verma.nipun@pgimer.edu.in.
*Nipun Verma and Arun Valsan contributed equally to this work as joint first authors.
†Nipun Verma, Arunaloke Chakrabarti, Nusrat Shafiq, and Ajay Duseja contributed equally to this work as joint senior authors.
Received October 13, 2025; accepted October 27, 2025; published online November 21, 2025

METHODS: **In this parallel-group, pragmatic, randomized trial with blinded endpoint adjudication (NCT04157465), 216 hospitalized ACLF patients with predefined host and clinical factors for IFI were randomized (1:1) to empirical antifungal therapy at enrolment or diagnostic/biomarker-driven-pre-emptive therapy on laboratory, radiological, or mycological confirmation. Biomarker-guided and culture-guided antifungal stewardship protocols were implemented in both groups. The primary outcome was 28-day overall survival. Secondary outcomes included in-hospital mortality, changes in severity scores, adverse events, and cost-effectiveness. Heterogeneous treatment effects were explored through causal tree analysis.**

RESULTS: **Empirical antifungal therapy significantly improved 28-day survival compared with diagnostic/biomarker-driven-pre-emptive therapy (35% vs 13%; hazard ratio: 0.64, 95% confidence interval: 0.47–0.88; $P = 0.005$). Treatment success (37.4% vs 16.9%; $P = 0.002$) and IFI resolution (45.8% vs 22.5%, $P = 0.001$) were higher; in-hospital and IFI-attributable mortality (55.6% vs 75.9%; $P = 0.003$) was lower in the empirical group. Fewer adverse events with greater quality-of-life years gains (29.9 vs 10.1) and an incremental cost-effectiveness ratio of international normalized ratio 1,42,737 were observed with empirical therapy. The survival benefit was maximum among patients aged 40 years or older with cardiovascular failure but without respiratory failure.**

DISCUSSION: **Early empirical antifungal therapy within a structured stewardship framework improves survival in patients with ACLF and IFIs. Timely recognition, rapid diagnostics, and individualized antifungal strategies are essential to bridge these high-risk patients toward recovery or definitive therapies.**

KEYWORDS: acute-on-chronic liver failure; cirrhosis; invasive fungal infections; mortality

ABBREVIATIONS: ACLF, acute-on-chronic liver failure; AD, acute decompensation; APASL, Asian Pacific Association for the Study of the Liver; BDG, beta-D-glucan; CI, confidence intervals; CLIF-C ACLF, Chronic Liver Failure Consortium-ACLF score; CLIF-C OF, Chronic Liver Failure Consortium-Organ Failure score; EASL, European Association for the Study of the Liver; GMI, Galactomannan Index; HR, hazard ratio; ICER, incremental cost effectiveness ratio; ICU, intensive care unit; IFI, invasive fungal infection; IQR, interquartile range; LAMB, liposomal amphotericin B; MELD, Model for End-Stage Liver Disease; MELD-NA, Model for End-Stage Liver Disease-Sodium; QALY, quality-adjusted life years; UTI, urinary tract infection; VAP, ventilator-associated pneumonia

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D830

Am J Gastroenterol 2025;00:1–13. https://doi.org/10.14309/ajg.0000000000003832

INTRODUCTION

Immunoparesis (1), broad-spectrum antimicrobial exposure, organ failures, invasive procedures, and high disease severity invite invasive fungal infections (IFIs) in cirrhosis (2,3). IFIs are often nosocomial and follow bacterial infections (4). They confer progression from acute decompensated (AD) to acute-on-chronic liver failure (ACLF), intensive care unit (ICU) admission, transplant delisting, and exuberant costs (5,6). Their prevalence varies (1%–47%) according to geography, income status of the country, risk factors, and diagnostic criteria (3,7). Candidiasis, aspergillosis, cryptococcosis, and mucormycoses are the commonly reported IFIs in cirrhosis (8,9). Mortality is high overall (50%–60%) and higher in ACLF, ICU care, aspergillosis, and *Candida* peritonitis (4,5,8–10).

The key reasons for poor outcomes in cirrhosis patients with IFIs include poor suspicion, diagnostic and treatment delays that confer progression, and multiorgan failures (11). Unlike bacterial infections, IFIs present with nonspecific signs and symptoms (12). Mycological cultures have limited sensitivity (25%–30%) and slow turnaround times (up to 14 days for specific cultures) (12). Acquiring invasive tissues for definite diagnosis is challenging because of the fragile status of patients, coagulopathy, and hemodynamic alterations (2,12,13), thus impeding an appropriate early treatment. Surrogate biomarkers: beta-D-glucan (BDG) and galactomannan are available for diagnosing IFIs (14), but limited literature supports their utility for ruling-in cases, mainly remaining as the markers of exclusion (15,16).

In the medical population, the Infectious Diseases Scoiety of America recommends antifungals in clinically suspected high-risk patients (17). Recent global guidelines on candidiasis recommend empirical antifungals in critically ill at-risk patients demonstrating septic shock or clinical deterioration (18). While for diagnosing aspergillosis, a robust multimodal approach combining clinical (cough), radiologic (nodules), bronchoscopic (eschar), and mycological evidence (galactomannan or mycological cultures) is recommended (19). The treatment, however, is open to clinical judgement (19). Studies supporting empirical treatment based solely on clinical suspicion confer risk of overuse, toxicities, and emergence of drug resistance (19). A more confirmatory, diagnostic/biomarker-driven-pre-emptive strategy based on radiology, biomarkers, and mycological cultures is an alternative to avoid such risks (19). Moreover, some physicians believe in treating microbiologically proven infections, while others advocate for prophylaxis, especially in peritransplant settings (20). Thus, ongoing uncertainty about a practical approach to treat IFIs in cirrhosis represents a state of clinical equipoise.

Currently, the ACG advises suspicion for fungal pathogens when hospitalized ACLF patients with bacterial infection do not

respond to antibiotics (2). The American Association for the Study of Liver Diseases recommends broadening coverage for antifungals for nosocomial infections or ACLF not improving on appropriate antibiotics after 48 hours (21). The European Association for the Study of Liver (EASL) recommends empirical antifungals in at-risk ACLF patients with nosocomial septic shock (6). However, such recommendations are based primarily on expert opinions based on observational studies. No randomized trial has addressed the optimal strategy for treating IFIs in ACLF. Hypothesizing the likelihood of benefit with early treatment with early stopping rules in those without any evidence, this randomized controlled trial compared the efficacy and safety of early empirical (suspicion-based) with a diagnostic/biomarker-driven-pre-emptive (mycological, radiological, or laboratory-based confirmation) antifungal strategy in patients with ACLF.

METHODS

This study was a pragmatic, parallel-group, open-label, randomized controlled trial with blinded endpoint assessments (prosepective, randomised, open label, blinded endpoint design), performed at a high-burden setting at a large tertiary care institute with dedicated hepatology services in India between November 7, 2019, and December 31, 2024. The trial was prospectively registered on ClinicalTrials.gov (NCT04157465) and received approval from the Institutional Ethics Committee (PGI/IEC/2019/001924). Written informed consent was obtained from all patients or their legally authorized representatives. The study followed the Good Clinical Practice Guidelines and Guidelines for Biomedical Research in Humans by the Indian Council of Medical Research. The Consolidated Standards of reporting Trials 2025 guidelines were followed for the trial reporting, and the trial protocol, statistical analysis plan, and key definitions of variables are provided in the Supplementary Digital Content (see Supplementary Appendix, http://links.lww.com/AJG/D830).

Participants

Eligible participants were adults (≥18 years of age) with a diagnosis of ACLF based on the European Association for the Study of Liver (EASL) or Asian Pacific Association for the Study of the Liver (APASL), along with a suspicion of IFI, defined using a combination of host (risk) and clinical criteria. Participants were required to have a minimum of ICU stay exceeding 48 hours or recent hospitalization for the current illness, along with at least 2 additional risk factors for IFIs, such as mechanical ventilation, broad-spectrum antibiotic use, central venous catheters, diabetes, malnutrition, high-severity scores, renal replacement therapy, and at least 1 clinical criterion suggestive of IFI. Clinical criteria included persistent sepsis (rise in Sequential Organ Failure score of 2 or more from baseline) or systemic inflammatory response syndrome despite appropriate broad-spectrum antimicrobials, recurrence of fever despite antimicrobial therapy, unexplained worsening of organ functions, or characteristic symptoms or signs suggestive of fungal involvement of the respiratory tract, sinuses, skin, central nervous system, or any other site. The key exclusion criteria were neutropenia, recent antifungal therapy, HIV seropositivity, pregnancy, hepatocellular carcinoma, and moribund status with 4 or more organ failures. A detailed list of inclusion and exclusion criteria is available in the Supplementary Digital Content (see Supplementary Tables 1 and 2, http://links.lww.com/AJG/D830).

Randomization and interventions

Patients were randomized in a 1:1 ratio using a computer-generated randomization sequence, with allocation concealed through sequentially numbered, opaque sealed envelopes by an independent pharmacologist. Participants in the empirical group received systemic antifungal therapy at the time of randomization based solely on risk factors and clinical criteria. In the diagnostic/biomarker-driven-pre-emptive group, antifungals were initiated only after predefined diagnostic criteria—radiological-based, mycological-based, or biomarker-based—and confirmed the presence of IFI (see Supplementary Table 3, http://links.lww.com/AJG/D830). The treating physicians were unaware of the allocation sequence. The suspected site of infections was adapted according to EASL guidelines (see Supplementary Table 4, http://links.lww.com/AJG/D830) (6). The baseline data, including demographics, etiology, disease severity, risk factors, clinical variables, organ support, and treatment, were collected at randomization in both groups.

The treating physicians in both groups made the pragmatic decision to choose antifungal agents. Liposomal amphotericin B (LAMB) was the most commonly used agent, administered at 3–5 mg/kg body weight as a 4-hour infusion in 5% dextrose. The injection was prepared 10 minutes before the administration. For the initial dose, 1 mg was infused over 10 minutes using a microdrip set, which was then observed for 30 minutes for any local reactions. If tolerated, the remaining dose of the drug was administered. In case of intolerance or contraindications to LAMB, the patients received rescue or salvage treatment as per the guidelines (see Supplementary Table 5, http://links.lww.com/AJG/D830). All patients received standard medical therapy according to the EASL guidelines, including rifaximin, lactulose, bowel wash, albumin, targeted antibiotics, and organ support (2,6).

Stewardship decisions: Duration and cessation of antifungal therapy were determined by predefined criteria (see Supplementary Table 6, http://links.lww.com/AJG/D830), incorporating clinical response, biomarker trends, and fungal culture results, adapted from the literature (15,16). The patients were monitored daily with standard investigations and scheduled follow-ups till 28 days, liver transplant, or death (see Supplementary Table 7, http://links.lww.com/AJG/D830).

Outcomes

The primary outcome was 28-day overall survival in the intention-to-treat population, including all those randomized in the trial. Secondary outcomes within the 28-day frame included in-hospital mortality; changes in liver disease severity scores—Model for End-Stage Liver Disease (MELD), MELD-Sodium, and Chronic Liver Failure Consortium-Organ Failure and ACLF (CLIF-C OF and CLIF-C ACLF); trends in fungal biomarkers (BDG and galactomannan index); mechanical ventilation-free days; length of ICU and hospital stay; incidence of nosocomial infections (including ventilator-associated pneumonia, urinary tract infections, and fungal peritonitis); frequency of adverse and serious adverse events; and cost-effectiveness of therapies.

Adverse events were monitored daily by a research fellow unaware of group allocation, severity was graded with Commom Terminology Criteria for Adverse Events.v5 guidelines, and causality were ascertained by World Health Organisation - Uppsala Monitoring Centre criteria by a blinded pharmacologist. An independent, institutional board, external to the treating teams and blinded to treatment allocation, reviewed IFI-related

mortality and other endpoints. All IFI-related deaths were classified as serious adverse events and underwent quarterly review by the committee (physicians, clinical pharmacologists, and research methodologists). Cost analysis was performed using direct and indirect medical costs with quality-of-life years (QALY) gained in each group. A team of 2 health economists performed the analysis. The detailed definitions of all outcomes are provided in the Supplementary Digital Content (see Supplementary Table 8, http://links.lww.com/AJG/D830).

Sample size estimation

Based on prior data indicating a 28-day survival rate of 46% in the empirical group and 27% in the diagnostic/biomarker-driven-pre-emptive group (22), a sample size of 198 patients (99 per group) was calculated with 80% power and a 2-sided alpha of 0.05. This size was sufficient to detect a hazard ratio of 0.6 with the same power assumptions. To account for an anticipated 10% attrition, the final sample size was 216 patients (108 per group).

Statistical analysis

All analyses were performed using SPSS v.22 and RStudio v.1.4.1103. Continuous variables were summarized as mean (SD) or median (interquartile range [IQR]) based on data distribution by the Shapiro-Wilk test. Categorical variables were expressed as frequencies and percentages. Missing data were not imputed. End-of-treatment values for secondary outcomes were used for comparisons. Between-group comparisons for categorical variables were performed using the χ^2 or Fisher exact test. By contrast, continuous variables were compared using the appropriate independent *t* test or Mann-Whitney *U* test. The primary endpoint, 28-day survival, was analyzed using Kaplan-Meier survival curves, with comparisons between groups assessed using the log-rank test. Death was considered an event, while patients who were alive, discharged, or had undergone transplantation were censored at the corresponding time point. Multivariable Cox proportional hazards regression was used to adjust for baseline disease severity indicators, including MELD score, CLIF-C OF score, and EASL-ACLF grade. The hazard ratios (HR) with 95% confidence intervals (CIs) were reported. The proportional hazards assumption was assessed using Schoenfeld residuals. A significant time-varying effect was considered a violation of the proportional hazard assumption. In the presence of such a violation, treatment effect estimates were complemented by analysis of restricted mean survival time. In addition, landmark analyses at days 7, 14, 21, and 28 were performed, with survival compared from each landmark onward using the log-rank test. The Wilcoxon signed-rank and Mann-Whitney *U* tests assessed within-group and between-group changes in severity scores and biomarker levels from baseline to end-of-treatment. Cost-effectiveness analysis was evaluated by calculating the incremental cost-effectiveness ratio (ICER), which is defined as the total direct and indirect medical costs between the empirical and diagnostic/biomarker-driven-pre-emptive arms divided by the difference in QALYs gained within the 28 days. QALYs were estimated using EuroQol 5-dimension-derived utility scores with local validation (23) applied to 28-day survival outcomes (see Supplementary Table 8, http://links.lww.com/AJG/D830). All statistical tests were 2-sided, and a P value of <0.05 was considered statistically significant.

Subgroup analysis was performed to explore the consistency of the treatment effect across key clinical subgroups, AD and ACLF (per EASL criteria, as all patients with APASL-ACLF satisfied the criteria for AD), baseline MELD score ($\geq$30 vs $<$ 30), and number of organ failures ($\geq$2 vs $<$ 2). Interaction terms were tested to evaluate potential effect modification in cox regression. No multiplicity adjustments were applied because of the exploratory nature of these analyses.

Treatment-effect heterogeneity assessments

A causal tree analysis was conducted to explore patient subgroups that derived the greatest benefit from empirical antifungal therapy. The model was developed using the causalTree package in R, which estimates heterogeneous treatment effects across different clinical profiles rather than just the average treatment effect. To reduce overfitting and improve reliability, an honest splitting approach was used, splitting the data set into separate parts for building the tree structure and for estimating treatment effects. The model's complexity parameter was tuned using cross-validation to minimize prediction error, and the final tree was pruned (optimal complexity parameter) accordingly for optimal interpretability. This analysis revealed clinically meaningful subgroups with variable responses to empirical therapy, providing insights into which patients may benefit most and supporting a move toward personalized antifungal strategies in ACLF.

RESULTS

Baseline characteristics

Of the 487 patients screened for eligibility, 216 patients with ACLF and suspected IFIs were enrolled and randomized in a 1:1 ratio (108 per group) (Figure 1). All participants were followed for 28 days, or until death or liver transplantation, whichever occurred first. However, none could undergo the transplant. The 2 study arms were well-balanced in demographics and clinical characteristics. The median age of participants was 41.5 years (IQR: 34–49.5) in the empirical group and 43.0 years (IQR: 35–50.0) in the diagnostic/biomarker-driven-pre-emptive group ($P = 0.521$). The cohort was predominantly male (92%). Alcohol-related cirrhosis 172 (79.6%) was the most common underlying etiology, and infection 135 (62.5%) and alcohol-related hepatitis 150 (69.4%) were the leading acute precipitants. A total of 87.5% of patients met EASL-ACLF criteria, while remaining 12.5% patients satisfied the APASL-ACLF or EASL-AD criteria. Baseline disease severity scores, organ failure profiles, bacterial infections, antimicrobials, laboratory parameters, IFI risk factors, and suspected sites of infection were comparable between groups (Table 1 and see Supplementary Table 9, http://links.lww.com/AJG/D830).

Treatment details. The median duration between admission and randomization was 4 days (IQR: 2–8). In the empirical group, of 108, 107 patients (99%) received antifungals at randomization, primarily LAMB (88.8%), anidulafungin (13.0%), and fluconazole (0.9%). In the diagnostic/biomarker-driven-pre-emptive group, antifungal was initiated on meeting biomarker, microbiological, or imaging criteria (see Supplementary Table 3, http://links.lww.com/AJG/D830); 89/108 (82.4%) received therapy with LAMB (74%), anidulafungin (8.3%), and fluconazole (1.9%). Nineteen patients were untreated because nonfulfillment of criteria, logistics, or early death/discharge. The median time to therapy from admission was 7.5 days (IQR 4–11.8); the median delay from randomization was 3 days (IQR 1–4) in the diagnostic/biomarker-driven-pre-emptive group. However, the median duration of antifungal treatment was similar in both groups,

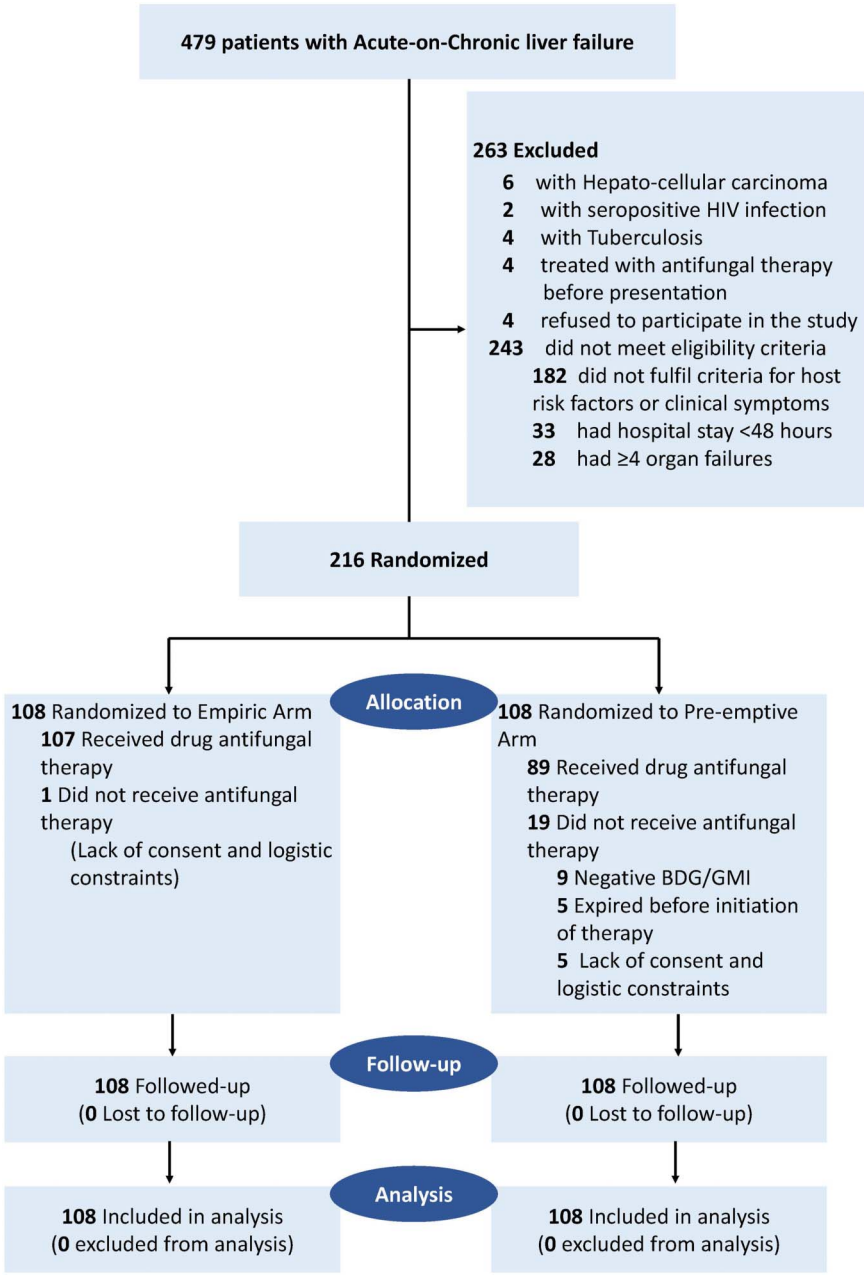


Figure 1. CONSORT flow diagram of the trial. The flow diagram illustrates the number of patients screened, enrolled, randomly assigned, and followed up in each study group. CONSORT, consolidated standards of reporting trials.

8 days (IQR: 5–14 days vs 5–12 days in empirical vs diagnostic/biomarker-driven-pre-emptive).

Concomitant care included broad-spectrum antibiotics (99%), invasive lines (75.9%), vasopressors, ventilatory support, and albumin or terlipressin as needed. Bacterial and multidrug-resistant bacterial infections were frequent and were similarly distributed across groups (Table 1 and see Supplementary Table 9, http://links.lww.com/AJG/D830).

Stewardship. Using clinical evaluation, fungal cultures, and biomarkers (BDG, galactomannan index), we were able to de-escalate antifungal therapy in 42 patients (19.4%; 21.3% and 17.6% in empirical and diagnostic/biomarker-driven-pre-emptive groups, respectively), thereby ensuring antifungal stewardship during the trial.

Primary outcome

At 28 days, the overall survival was significantly better in the empirical group (38 patients; 35%) compared with the diagnostic/biomarker-driven-pre-emptive group (14 patients; 13%; $P = 0.005$) (Figure 2a), corresponding to an absolute mortality difference of −22.2% (95% CI: −11.2 to −33.2) and number needed to treat of 5 (rounded up from 4.5, 95% CI: 3–9). Cox regression confirmed significantly lower mortality in the empirical group (HR: 0.64; 95% CI: 0.47–0.88; $P = 0.005$) (Table 2). This survival benefit was significant when adjusting for baseline severity scores, including CLIF-C OF (adjusted HR: 0.64), MELD score (HR: 0.63), and ACLF grade (HR: 0.64), $P < 0.05$, each.

Table 1. Characteristics of patients in the trial population

Characteristics	Empirical (n = 108)	Pre-emptive (n = 108)	*P* value
Age (yr)	41.5 (34.0–49.5)	43.0 (35.0–50.0)	0.521
Sex, male (n, %)	101 (93.5)	98 (90.7)	0.613
EASL-ACLF grade (n, %)			0.365
Grade 0	11 (10.2)	16 (14.8)	
Grade I	31 (28.7)	23 (21.3)	
Grade II	41 (38)	37 (34.3)	
Grade III	25 (23.1)	32 (29.6)	
Etiology of cirrhosis			
ALD/MASLD/viral/others	87/2/3/26	85/5/3/28	0.598
Vitals			
Pulse (beats/min)	100.5 (92.0–114.0)	102.0 (94.0–114.0)	0.450
MAP (mm Hg)	84.2 (77.2–90.9)	85.0 (77.6–92.7)	0.593
RR (per min)	22 (21–24)	22 (20–24)	0.447
Laboratory investigations			
Hemoglobin (gm/dL)	8.1 (7.1–9.4)	8.1 (7.0–9.2)	0.449
TLC ($^{c}10^{6}$ cells/mm^{3})	14.8 (9.4–22.4)	14.9 (9.9–21.1)	0.888
Platelet count ($^{c}10^{6}$ cells/mm^{3})	98.0 (65.5–148.5)	83.0 (54.0–135.5)	0.178
Creatinine (mg/dL)	1.6 (0.8–2.6)	1.5 (1.0–2.7)	0.588
Bilirubin (mg/dL)	17.5 (7.4–29.2)	15.8 (7.0–26.0)	0.331
ALT (IU/L)	43.0 (30.3–76.8)	43.0 (27.0–69.5)	0.200
Albumin (g/dL)	2.9 (2.7–3.3)	2.8 (2.5–3.2)	0.103
INR	2.1 (1.7–2.6)	2.1 (1.7–2.7)	0.832
Procalcitonin (ng/mL)	0.8 (0.5–1.8)	1.1 (0.5–2.6)	0.578
BDG (pg/mL)	195 (55.2–326.8)	146 (52.5–245.8)	0.184
GMI	0.5 (0.3–0.9)	0.6 (0.3–1.1)	0.359
Lactate (mmol/L)	2.3 (1.6–3.1)	2.5 (1.8–3.4)	0.169
Vasopressor use (n, %)	12 (11.1)	17 (15.9)	0.409
Ventilator use (n, %)	27 (25)	32 (29.6)	0.541
Albumin use (n, %)	80 (74.1)	75 (69.4)	0.545
Terlipressin use (n, %)	33 (30.6)	28 (25.9)	0.545
Severity scores			
MELD-Na	31.4 (27.4–35.6)	31 (25.5–35.6)	0.573
CLIF-C OF	12 (11–13)	12 (11–13)	0.255
CLIF-C ACLF	52.8 (48.1–57.5)	54.4 (48.1–61.4)	0.223
Risk factors (n, %)[a]			
Mechanical ventilation	28 (25.9)	36 (33.3)	0.297
Broad-spectrum antibiotics	107 (99.1)	107 (99.1)	1.000
Invasive lines	82 (75.9)	82 (75.9)	1.000
Diabetes mellitus	13 (12.0)	13 (12.0)	1.000
Parenteral nutrition	1 (0.9)	2 (1.9)	1.000
Hemodialysis	12 (11.1)	10 (9.3)	0.822
Pancreatitis-related admission	1 (0.9)	3 (2.8)	0.614
Steroid or immunosuppressants use	4 (3.7)	4 (3.7)	1.000
MELD ≥20 or APACHE-II ≥16	101 (93.5)	99 (91.7)	0.795
Refractory ascites on norfloxacin	65 (60.2)	60 (55.6)	0.581

Table 1. (*continued*)

Characteristics	Empirical (n = 108)	Pre-emptive (n = 108)	*P* value
GI surgery or leaks	8 (7.4)	3 (2.8)	0.216
COPD/TB	0 (0.0)	3 (2.8)	0.245
Moderate to severe sarcopenia	89 (82.4)	86 (79.6)	0.729
Recent influenza	1 (0.9)	1 (0.9)	1.000
Clinical criteria (n, %)[a]			
Unresolved sepsis or SIRS on antibiotics	108 (100)	108 (100)	1.000
Fever relapse on antibiotics	55 (50.9)	45 (41.7)	0.219
Tracheobronchial lesions	6 (5.6)	14 (13.0)	0.100
Sino-nasal infection	0	0	
Respiratory worsening on antibiotics	32 (29.6)	26 (24.1)	0.443
Pleuritic pain, rub, dyspnoea, hemoptysis	1 (0.9)	1 (0.9)	1.000
Suspected skin lesions	0 (0.0)	1 (0.9)	1.000
Unexplained or worsening HE	19 (17.8)	20 (18.5)	1.000
Type of IFI (n, %)[b]			
Possible	13 (12)	13 (12)	0.929
Probable	91 (84.3)	92 (85.2)	
Proven	3 (2.8)	4 (3.7)	
Candida spp	2	3	
Aspergillus spp.	0	1	
Suspected site of IFI (n, %)[b,c]			
UTI	2 (1.9)	2 (1.9)	0.897
Peritoneal	1 (0.9)	1 (0.9)	
SSTI	0 (0.0)	1 (0.9)	
Pneumonia	40 (37.0)	35 (32.4)	
Spontaneous infection	42 (38.9)	47 (43.5)	
Unclear	23 (21.3)	22 (20.4)	
Antifungals therapy (n, %)			
LAMB	96 (88.8)	80 (74)	0.001
Anidulafungin	14 (13)	9 (8.3)	
Fluconazole	1 (0.9)	2 (1.9)	
Not administrated	1 (0.9)	19 (17.6)	
Days between admission and randomization	4 (2–8)	4 (2–8)	0.544
Days between admission and start of antifungals	4 (3–9.5)	7.5 (4–11.8)	0.002
Days between randomization and start of antifungals	0	3 (1–4)	<0.001
Duration of antifungals (d)	8 (5–14)	8 (5–12)	0.765
Antifungal de-escalation	23 (21.3%)	19 (17.6%)	0.606

Data are presented as median (IQR) or number (percentage) as suitable. Numerical data were compared between the groups using Mann-Whitney *U*-test, and categorical data were compared using the χ^2 test. $P < 0.05$ was considered significant.
[a]Detailed risk and clinical criteria are given in the Supplementary Digital Content (see Ssupplementary Table 1, http://links.lww.com/AJG/D830).
[b]Ascertained after randomization and allocation with culture and biomarker reports.
[c]Suspected site was marked according to the criteria in the Supplementary Digital Content (see Supplementary Table 4, http://links.lww.com/AJG/D830).
ACLF, acute-on-chronic liver failure; ALD, alcohol-associated liver disease; ALT, alanine aminotransferase; APACHE-II, Acute Physiology and Chronic Health Evaluation II; APASL, Asian Pacific Association for the Study of the Liver; BDG, beta-D-glucan; CLIF-C ACLF, CLIF Consortium ACLF score; CLIF-C OF, Chronic Liver Failure Consortium-Organ Failure score; COPD, chronic obstructive pulmonary disease; EASL, European Association for the Study of the Liver; GI, gastrointestinal; GMI, galactomannan index; HE, hepatic encephalopathy; IFI, invasive fungal infection; INR, international normalized ratio; LAMB, liposomal amphotericin B; MAP, mean arterial pressure; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD-Na, Model for End-Stage Liver Disease With Sodium; RR, respiratory rate; SIRS, systemic inflammatory response syndrome; SSTI, skin and soft tissue infection; TB, tuberculosis; TLC, total leukocyte count; UTI, urinary tract infection.
Extended data are provided in the Supplementary Digital Content (see Supplementary Table 9, http://links.lww.com/AJG/D830).

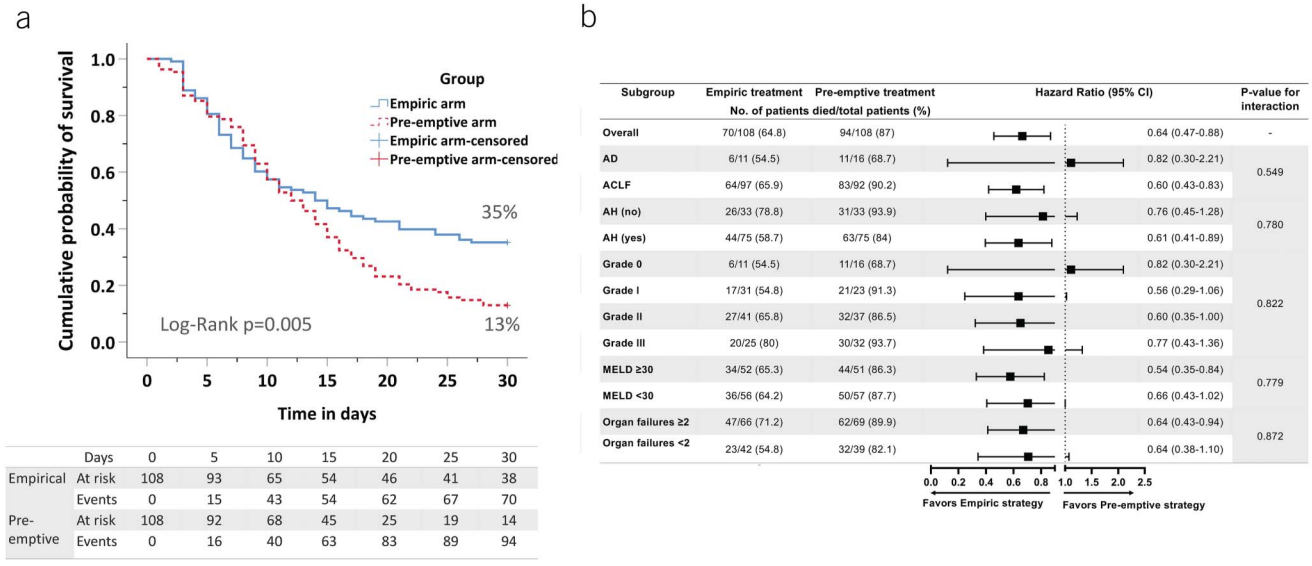


Figure 2. Survival outcomes and subgroup analysis. (**a**) Kaplan-Meier curves comparing 28-day survival between the empirical and diagnostic/biomarker-driven-pre-emptive antifungal treatment groups. Survival probabilities were compared using the log-rank test with $P < 0.05$ as significant. Numbers at risk and cumulative events are displayed below the graph. (**b**) Forest plot showing hazard ratios (HRs) for 28-day mortality across predefined clinical subgroups, comparing empirical vs diagnostic/biomarker-driven-pre-emptive antifungal therapy. An HR < 1 favors empirical therapy. Subgroups include ACLF presence as defined by EASL, MELD score (<30 vs ≥30), and number of organ failures (<2 vs ≥2). Squares represent effect sizes, and error bars indicate 95% confidence intervals (95% CI), *P* values for interaction; <0.05 are significant. ACLF, acute-on-chronic liver failure; EASL, European Association for the Study of the Liver; MELD, Model for End-Stage Liver Disease.

However, Schoenfeld residuals indicated violation of the proportional hazard assumption (global test $P = 0.001$). Accordingly, we complemented the Cox analysis with (restricted mean survival time) up to 28 days: Empirical therapy yielded +2.5 days (95% CI 0.04–5.0; $P = 0.046$) more mean survival than diagnostic/biomarker-driven-pre-emptive therapy. In landmark analyses, survival curves diverged significantly from day 7 onward (log-rank $P < 0.001$ at day 7 and day 14; $P = 0.015$ at day 21; $P = 0.028$ at day 28), consistent with a delayed treatment effect.

The highest mortality was observed among patients with grade III ACLF (HR: 2.49; 95% CI: 1.43–4.32, $P = 0.001$). The leading causes of death, refractory septic shock, and multiorgan failures were comparable between groups ($P = 0.625$). However, the IFI-attributable mortality was significantly lower in the empirical group (60 patients; 55.5%) compared with the diagnostic/biomarker-driven-pre-emptive group (82 patients; 75.9%, $P = 0.003$) (Table 3). Consistently, a significantly greater proportion of patients in the empirical arm achieved clinical resolution of IFI (45.8% vs 22.5%, $P = 0.001$). These findings indicate that the survival benefit with empirical antifungal therapy was primarily driven by improved IFI control.

Secondary outcomes

On follow-up, the in-hospital mortality was lower in the empiric group (55.6% vs 71.3%, $P = 0.024$) (Table 3). The empirical group exhibited significantly lesser progression of organ failures, particularly in CLIF-C ACLF scores ($P = 0.034$) (see Supplementary Table 10, http://links.lww.com/AJG/D830), and a lesser delta increase in MELD-Sodium ($P = 0.031$), see Supplementary Table 11, http://links.lww.com/AJG/D830. There was a trend of improvement in BDG levels in the empirical group ($P = 0.094$), whereas no difference was observed in the diagnostic/biomarker-driven-pre-emptive group ($P = 0.797$), see Supplementary Table 12, http://links.lww.com/AJG/D830. Thirty-eight patients (35.2%) in the empirical arm remained free of ventilator support compared with 14 patients (13.0%) in the diagnostic/biomarker-driven-pre-emptive arm, indicating significantly less ventilator dependence with empirical therapy ($P < 0.001$). The median number of ventilator-free days was numerically higher in the empirical group than the diagnostic/biomarker-driven-pre-emptive group (8.5 [IQR 3.0–27.0] vs 7.0 [IQR 2.8–15.2] [$P = 0.065$]). Median ICU stay was shorter in the empirical group (6.0 days [IQR: 3.0–10.0]) as compared with the diagnostic/biomarker-driven-pre-emptive group (8.0 days [IQR: 4.0–12.0], $P = 0.188$), although the difference was not statistically significant. Hospital length of stay was similar between the groups (10.0 days [IQR: 6.0–17.2] vs 11.0 days [IQR: 7.0–16.0], $P = 0.745$). The incidence of nosocomial infections, including VAP, fungal peritonitis, and urinary tract infection, did not differ significantly between the 2 groups (see Supplementary Table 13, http://links.lww.com/AJG/D830). However, treatment success rates were considerably higher in the empirical group (40 patients; 37.4%) than in the diagnostic/biomarker-driven-pre-emptive group (15 patients; 16.9%; $P = 0.002$), see Supplementary Table 14, http://links.lww.com/AJG/D830.

Adverse events

The empirical group experienced fewer adverse events (90.7% vs 99.1%; $P = 0.013$), with a lower mean number of adverse events per patient (2.2 vs 2.6; $P = 0.041$). Serious adverse events, including septic shock and death, were more frequent in the diagnostic/biomarker-driven-pre-emptive group ($P < 0.05$ for each). Treatment-emergent nonserious adverse events were similar between the 2 groups, mainly grades I to II, and related to

Table 2. Cox regression demonstrating impact of treatment on mortality in the trial population

Univariable	HR	95% CI	*P* value
Treatment strategy (empirical vs pre-emptive)	0.64	0.47–0.88	0.005
Multivariable models			
Model 1			
Treatment strategy	0.64	0.47–0.88	0.006
CLIF-C OF	1.19	1.09–1.30	<0.001
Model 2			
Treatment strategy	0.65	0.47–0.88	0.006
SOFC	1.30	1.12–1.51	0.001
Model 3			
Treatment strategy	0.63	0.46–0.87	0.004
MELD	1.01	0.99–1.03	0.368
Model 4			
Treatment strategy	0.64	0.46–0.87	0.005
ACLF grade I	1.37	0.77–2.44	0.282
ACLF grade II	1.68	0.97–2.89	0.062
ACLF grade III	2.49	1.43–4.32	0.001
Model 5			
Treatment strategy	0.64	0.47–0.88	0.006
Days between admission and randomization	0.99	0.96–1.03	0.690
Model 6			
Treatment strategy	0.59	0.40–0.86	0.006
Days between admission and initiation of antifungals	0.93	0.87–1.00	0.060

Data are presented as HR and 95% CI, multivariable cox-proportional hazard regression was used, $P < 0.05$ was considered as significant.
ACLF, acute-on-chronic liver failure; CI, confidence intervals; CLIF-C OF, Chronic Liver Failure-Organ Failure score; HR, hazard ratio; MELD, Model for End-Stage Liver Disease; SOFC, standard-of-care failure criteria.

underlying illness or drugs used. Treatment discontinuation due to toxicity (seizures) occurred in 2 patients in the empirical group and 3 in the diagnostic/biomarker-driven-pre-emptive group ($P = 0.835$). The detailed data on adverse events, grades, and causality in each group are provided in Table 4 and Supplementary Digital Content (see Supplementary Table 15, http://links.lww.com/AJG/D830). Additional analysis among patients who received at least 1 dose of antifungals revealed consistent observations of adverse events between the groups (see Supplementary Table 16, http://links.lww.com/AJG/D830).

Cost-effectiveness

Empirical antifungal therapy incurred a modestly higher per-patient cost of $2,607 (international normalized ratio [INR] 228,782) vs $2,309 (INR 202,669), an incremental difference of $296 (INR 26,000). Despite the higher cost, empirical therapy yielded a substantially greater QALY gain (29.9 vs 10.1), resulting in an ICER of $1,626 per QALY gained (INR 142,737 per QALY). This ICER falls well within a commonly cited willingness-to-pay threshold of approximately $2,279 per QALY (one gross domestic product per capita in India; INR 200,000), supporting empirical therapy as a clinically and economically favorable option for patients with ACLF and suspected IFIs (see Supplementary Table 16, http://links.lww.com/AJG/D830). Currency conversions used 1 USD = 87.76 INR; sensitivity conclusions were unaffected by expressing costs in USD.

Treatment-effect heterogeneity

We compared survivors with nonsurvivors to explore patients who are likely to benefit from therapy. Survivors were more likely to be younger, had fewer risk factors for IFI, and had a lower prevalence of fever recrudescence on antibiotics, mechanical ventilation, and cerebral or respiratory failure before randomization. Notably, survivors received a longer duration of antifungal therapy compared with nonsurvivors (14 vs 7 days; $P < 0.001$) (see Supplementary Table 17, http://links.lww.com/AJG/D830).

Furthermore, a causal tree analysis identified the greatest survival benefit in patients without respiratory but with cardiovascular failure, especially in those aged 40 years or older, with an estimated treatment benefit of 91%. By contrast, no survival benefit was observed among patients with respiratory failure, highlighting the importance of individualized treatment strategies Figure 3 and Supplementary Digital Content (see Supplementary Table 18, http://links.lww.com/AJG/D830).

Subgroup analysis (Figure 2b) revealed a consistent benefit in 28-day mortality with empirical therapy across multiple relevant subgroups. Among patients with EASL-AD, mortality was 54.5%

Table 3. Reasons for mortality in the trial population

Event	Total (n = 216)	Empirical group (n = 108)	Pre-emptive group (n = 108)	*P* value
28-d mortality	164 (75.9)	70 (64.8)	94 (87)	<0.001
28-d IFI-attributable mortality	142 (65.7)	60 (55.6)	82 (75.9)	0.003
In-hospital mortality	137 (63.4)	60 (55.6)	77 (71.3)	0.024
Causes (n, % among nonsurvivors)				
RSS	123 (75)	53 (74.3)	71 (75.5)	0.625
MODS	14 (8.5)	6 (8.6)	8 (8.5)	
Cardiac arrest	5 (3)	1 (1.4)	4 (4.3)	
RSS + MODS	21 (12.8)	11 (15.7)	10 (10.6)	

Data are presented as number (percentage) and compared between the groups using the χ^2 test. $P < 0.05$ was considered significant.
IFI, invasive fungal infection; MODS, multiorgan dysfunction; RSS, refractory septic shock.

Table 4. Adverse events in the trial population

Event	Empirical group (n = 108)	Pre-emptive group (n = 108)	*P* value
Total no. of adverse events	237	277	
% patients with adverse event	98 (90.7)	107 (99.1)	0.013
Mean adverse events per patient	2.2 (1.3)	2.6 (1.3)	0.041
Serious adverse events, n (%)	74 (68.5)	94 (87)	0.002
Death	70 (64.8)	94 (87)	<0.001
Septic shock	63 (58.3)	81 (75)	0.014
Hypovolemic shock	10 (9.3)	18 (16.7)	0.156
Cardiac arrest	5 (4.6)	6 (5.6)	1.000
Treatment-emergent adverse events (nonserious)			
AKI	27 (25.0)	26 (24.1)	1.000
Hypokalaemia	26 (24.1)	25 (23.1)	1.000
ARD	21 (19.4)	16 (14.8)	0.470
Hyponatremia	12 (11.1)	16 (14.8)	0.543
Tachycardia	16 (14.8)	12 (11.1)	0.543
Hypotension	8 (7.4)	15 (13.9)	0.186
AMS (confusion/delirium)	13 (12.0)	14 (13.0)	1.000
Skin rashes/blisters/phlebitis	10 (9.3)	12 (11.1)	0.822
Fever or chills	7 (6.5)	8 (7.4)	1.000
Hyperkalaemia	2 (1.9)	8 (7.4)	0.105
Anxiety/insomnia	6 (5.6)	2 (1.9)	0.280
Nausea/constipation	3 (2.8)	5 (4.6)	0.719
Seizures	2 (1.9)	4 (3.7)	0.679
Tachypnoea	2 (1.9)	3 (2.8)	1.000
Abdominal pain	2 (1.9)	1 (0.9)	1.000
Bradypnea	1 (0.9)	2 (1.9)	1.000
Metabolic acidosis	0 (0.0)	2 (1.9)	0.477
Hypernatremia	0 (0.0)	1 (0.9)	1.000
Bradycardia	1 (0.9)	0 (0.0)	1.000

Data are presented as number (percentage) and compared between the groups using the χ^2 test. $P < 0.05$ was considered significant.
AKI, acute kidney injury; ARD, acute respiratory distress; AMS, altered mental sensorium.

vs 68.7% (HR: 0.82; 95% CI: 0.30–2.21). For those with EASL-ACLF, mortality was 65.9% vs 90.2% (HR: 0.60; 95% CI: 0.43–0.83). Patients with alcohol-associated hepatitis had a survival benefit (58.7% vs 84%; HR: 0.61; 95% CI: 0.41–0.89), while those without alcohol-associated hepatitis, the mortality was 78.8% vs 93.9% (HR: 0.76; 95% CI: 0.45–1.28). Among patients with EASL-ACLF grade 0, empirical therapy was associated with lower mortality (54.5% vs 68.7%; HR: 0.82, 95% CI: 0.30–2.21). In those with EASL-ACLF grade II, a clear survival benefit was observed with empirical therapy, with mortality of 65.8% compared with 86.5% (HR: 0.60, 95% CI: 0.35–1.00). In patients with MELD score ≥30, empirical therapy conferred a greater survival benefit (HR: 0.54; 95% CI: 0.35–0.84). The benefit was also evident in those with ≥2 failures (HR: 0.64; 95% CI: 0.43–0.94). Furthermore, no statistically significant interactions were observed across any subgroups, suggesting a consistent treatment effect of empirical therapy.

Patients who received LAMB, empirical therapy conferred a survival benefit compared with diagnostic/biomarker-driven-pre-emptive treatment, with lower 30-day mortality (69.6% vs 89%, $P = 0.002$), a significantly higher treatment success (33.7% vs 12.1%, $P = 0.001$), and resolution of IFI (40.2% vs 15.4%, $P < 0.001$). Excluding patients who remain untreated (1 in empiric and 19 in diagnostic/biomarker-driven-pre-emptive), the mortality was lower in the empiric group (65.4% vs 86.5%, $P = 0.001$).

DISCUSSION

This trial provides a framework of risk (host), clinical, and mycological factors for guiding treatment of IFIs in cirrhosis. It demonstrates the efficacy and safety of empirical over diagnostic/biomarker-driven-pre-emptive strategy in improving outcomes of patients with ACLF and suspected IFIs. Suspicion-based treatment in high-risk patients with stewardship guardrails was

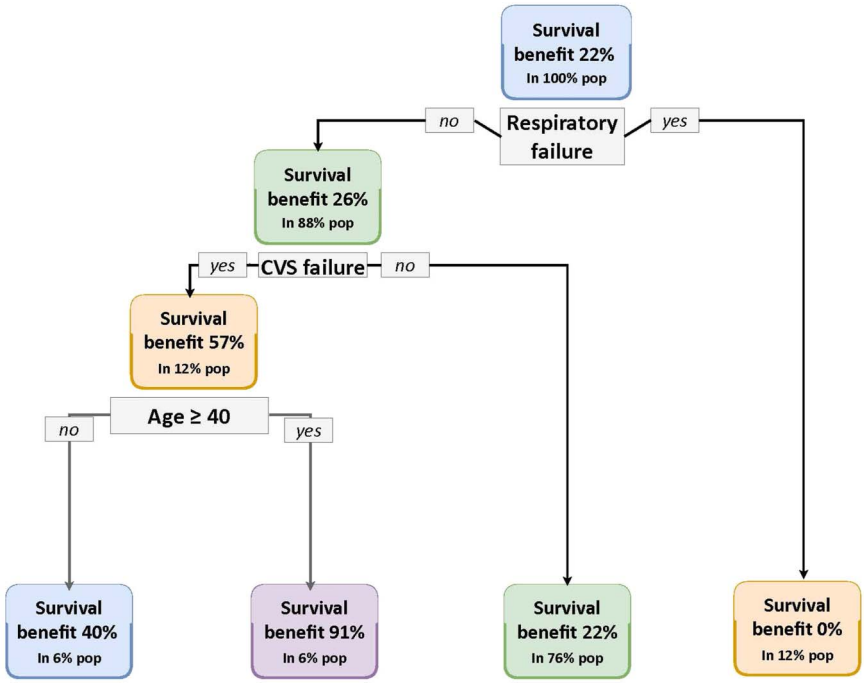


Figure 3. Causal tree analysis of treatment heterogeneity in the trial population. Causal tree model identifying subgroups of patients with differential benefit from empirical antifungal therapy. Key discriminating features include age and the presence of cardiovascular or respiratory failure in patients with acute-on-chronic liver failure (ACLF). The tree structure highlights clinical pathways associated with improved survival under empirical treatment.

found to be more effective than waiting for laboratory or radiological confirmation for treating IFIs in cirrhosis.

The findings align with the benefit of empiric therapy of IFIs in observational studies among immunocompromised and non-neutropenic ICU populations (24–26). An early empirical antifungal treatment has been linked with reduced mortality and improved outcomes in surgical ICU patients (27). One study reported lower mortality in candidemia cases when treated empirically within 12 hours of diagnosis (26). However, in the real world, the diagnosis through mycological cultures is often delayed (turnaround: 14 days for traditional Sabouraud agar and 72–120 hours for BD automated blood-culture detection system), reflecting the limited utility of culture-driven approach. A diagnostic/biomarker-driven-pre-emptive therapy seems more confirmatory, limiting overuse, but randomized trials do not support such recommendation (28) and observational data favor otherwise (25,26), especially in hematologic conditions (29). In nonneutropenic patients, a Cochrane review (30) showed the utility of untargeted antifungals vs placebo or no-treatment in reducing IFI risk by 45%. Such an untargeted group included a mix of prophylaxis, empirical, and diagnostic/biomarker-driven-pre-emptive approaches without clearly representing the cirrhosis population. Hence, our study was an unmet need to inform an optimal strategy for treating IFIs in cirrhosis.

The survival benefit in the empirical arm of our study possibly stems from avoiding treatment delays, which is evident from the median time from admission to antifungal initiation, which was 4 days in the empirical group and 7.5 days in the diagnostic/biomarker-driven-pre-emptive group. The delays were inevitable given the challenges in clinical presentation, poor yield of cultures, and logistic barriers for invasive samples. However, we believe that data suggest the mycological, laboratory, or radiological confirmations were essential for informing stewardship decisions and stopping antifungals in patients without any evidence of IFI.

Interestingly, the survival curve showing benefit with empirical therapy separated after 7 days in our trial. Possibly, it suggests the benefit of empirical therapy evident only after sustained exposure. This reflects that along with timely initiation, the adequacy of treatment duration, typically at least 7–14 days as supported by previous studies (14,19), is essential for translating antifungal activity into a measurable survival advantage.

Notably, the empirical therapy experienced fewer adverse events, including septic shock and treatment-related toxicity. Treatment success, defined by early resolution of sepsis, absence of new IFI, and without treatment-limiting toxicity, was more than twice as frequent in the empirical group (37.4% vs 16.9%). These results challenge the prevailing notion that an empirical antifungal strategy invariably leads to overtreatment, inappropriate exposure, or increased toxicity.

The economic analysis further supports the clinical benefit of early empirical therapy in ACLF patients with suspected IFIs. The empirical treatment yielded substantially greater QALY gains and an ICER well within accepted thresholds. To our knowledge, this is one of the first studies to evaluate the cost-effectiveness of antifungal strategies, specifically in ACLF in high-burden settings.

Identifying subgroups with differential effects represents an opportunity to advance personalized medicine. Younger patients with fewer risk factors, before respiratory or cerebral failure and progression to grade 3 ACLF, were likely to survive with antifungals in this study. The greatest benefit was observed in patients with cardiovascular failure and age 40 years or older. Although formal guidelines for sample size requirements in causal tree-

based heterogeneous-treatment-effect analyses are lacking, the findings should be interpreted cautiously, given the context and population reported in this study. Nevertheless, such observations resonate with global recommendations for early antifungal initiation in high-risk patients with septic shock (18) and highlight the need to identify phenotypes most likely to benefit.

This study's limitations merit discussion. The design was pragmatic and open-label; however, the primary outcome was an objective endpoint, and we did blinding of outcome assessments to mitigate potential biases. It was a single-center study with dedicated liver services, draining a broad referral area with a high burden of IFI, representing several healthcare systems in Asia and worldwide. Although alcohol-related hepatitis was leading acute-precipitant, only 5 patients received steroids and the results may not be as applicable, where the population composition is different. Nevertheless, it provides high-level evidence and strengthens the expert recommendations by the major societies (2,6,21,31). Although the empirical approach demonstrated clinical and economic advantages, in lower-acuity settings, the net benefit of empirical therapy may be smaller and indiscriminate use may foster resistance. The implementation should target predefined high-risk patients with clinical criteria with protocolized de-escalations. Similar de-escalations were performed in this study and have been considered safe in the literature (32,33). Despite the observed benefit, overall mortality across groups was high in our study, which highlights the fragile status of ACLF patients with IFIs. Proven IFI was rare, possibly due to low sensitivity of mycological cultures, limited availability of invasive samples due to safety concerns, and negative cultures due to early antifungals. Consequently, most cases did not meet proven criteria in this real-world setting. We believe there is an urgent, unmet need for early suspicion, rapid, point-of-care diagnostics to facilitate early and precise treatment of IFIs in ACLF.

In conclusion, early empirical antifungal therapy with integrated stewardship protocols significantly improved survival and treatment success in ACLF patients with IFIs without increasing the toxicity and at an acceptable cost. Future research should focus on refining risk stratification tools, developing host-phenotype, and molecular diagnostics-based antifungal algorithms to balance early interventions with stewardship practices.

ACKNOWLEDGMENTS

The paper will be presented during the Liver Meeting hosted by American Association for the Study of Liver Diseases in 2025. We gratefully acknowledge the support of the nursing staff, residents, fellows, and patients who contributed to this study.

CONFLICTS OF INTEREST

Guarantor of the article: Nipun Verma, MD, DM.

Specific author contributions: N.V.: conceptualization. N.V., A.V., P.G.: data curation. N.V., P.G., S.S.: formal analysis. N.V.: funding acquisition. N.V., A.C., N.S., A.V., S.S., S.P., N.M.: methodology. N.V., A.D., N.S.: project administration. N.V., A.D., A.C., S.P.: resources. N.V.: software. N.V., A.C., N.S., S.P.: validation. P.G., N.V.: visualization. N.V., A.V.: writing original draft. A.V., N.V., P.G., N.S., A.De., S.R., M.P.K., S.T., A.D.: writing review and editing.

Financial support: This work was funded by the Indian Council of Medical Research and awarded to Nipun Verma, Vide number 5/4/8–12/CD/NV/2021-NCD-II. The funders had no role in the trial's design, conduct, analysis, and reporting.

Potential competing interests: The authors declare no conflict of interest.

Study Highlights

WHAT IS KNOWN

- ✓ Invasive fungal infections are a significant cause of mortality in acute-on-chronic liver failure (ACLF), with reported prevalence between 15% and 48%, and mortality rates as high as 100% in some cohorts.
- ✓ Existing diagnostic methods are limited by low sensitivity and delayed turnaround times.
- ✓ International guidelines recommend empirical antifungal therapy in high-risk critically ill patients based on clinical suspicion; however, no randomized controlled trials had specifically evaluated the efficacy of empirical vs diagnostic/biomarker-driven-pre-emptive antifungal strategies in ACLF. Prior trials in general Intensive Care Unit populations have yielded inconclusive results regarding mortality benefit, and no study had definitively addressed this question in ACLF.
- ✓ There remains substantial uncertainty regarding the optimal antifungal strategy, particularly given the unique pathophysiology and high-risk profile of patients with ACLF.

WHAT IS NEW HERE

- ✓ Early empirical antifungals improved 28-day survival in ACLF with suspected invasive fungal infections.
- ✓ Empirical antifungal therapy reduced organ failure progression, ventilator dependence, and had higher treatment success (≥2 fold).
- ✓ Greater quality-adjusted life years gains and an ICER well within acceptable national thresholds, affirming its economic value.
- ✓ Causal-tree analysis showed maximal benefit in patients with ACLF 40 years or older with cardiovascular but not respiratory failure.

REFERENCES

1. Bajaj JS, Shawcross DL, Choudhury A, et al. Defining organ failures in patients with cirrhosis: Consensus statements. Gastroenterology 2025;169(5):1043–62.
2. Bajaj JS, O'Leary JG, Lai JC, et al. Acute-on-Chronic Liver Failure Clinical Guidelines. Am J Gastroenterol 2022;117(2):225–52.
3. Verma N, Singh S, Singh M, et al. Global epidemiological burden of fungal infections in cirrhosis patients: A systematic review with meta-analysis. Mycoses 2022;65(3):266–84.
4. Bajaj JS, Reddy RK, Tandon P, et al. Prediction of fungal infection development and their impact on survival using the NACSELD cohort. Am J Gastroenterol 2018;113(4):556–63.
5. Verma N, Singh S, Roy A, et al. Cirrhosis and fungal infections-a cocktail for catastrophe: A systematic review and meta-analysis with machine learning. Mycoses 2022;65(9):844–58.
6. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on acute-on-chronic liver failure. J Hepatol 2023;79(2):461–91.
7. Cao Z, Wong F, Choudhury AK, et al. Global prevalence and characteristics of infections and clinical outcomes in hospitalised patients with cirrhosis: A prospective cohort study for the CLEARED Consortium. Lancet Gastroenterol Hepatol 2024;9(11):997–1009.
8. Verma N, Roy A, Singh S, et al. Factors determining the mortality in cirrhosis patients with invasive candidiasis: A systematic review and meta-analysis. Med Mycol 2021;60(1):myab069.

9. Verma N, Singh S, Syal A, et al. Invasive aspergillosis is a critical determinant of mortality in cirrhosis: A systematic review with meta-analysis. Med Mycol 2021;59(11):1092–100.
10. Piano S, Singh V, Caraceni P, et al. Epidemiology and effects of bacterial infections in patients with cirrhosis worldwide. Gastroenterology 2019; 156(5):1368–80.e10.
11. Maiwall R, Piano S, Singh V, et al. Determinants of clinical response to empirical antibiotic treatment in patients with cirrhosis and bacterial and fungal infections-results from the ICA "Global Study" (EABCIR-Global Study). Hepatology 2024;79(5):1019–32.
12. Piano S, Angeli P. Current concepts on bacterial and fungal infections in cirrhosis. Clin Liver Dis (Hoboken) 2019;14(3):87–91.
13. Piano S, Bunchorntavakul C, Marciano S, et al. Infections in cirrhosis. Lancet Gastroenterol Hepatol 2024;9(8):745–57.
14. Verma N, Singh S, Taneja S, et al. Invasive fungal infections amongst patients with acute-on-chronic liver failure at high risk for fungal infections. Liver Int 2019;39(3):503–13.
15. Hanson KE, Pfeiffer CD, Lease ED, et al. β-D-glucan surveillance with preemptive anidulafungin for invasive candidiasis in intensive care unit patients: A randomized pilot study. PLoS One 2012;7(8):e42282.
16. De Rosa FG, Corcione S, Montrucchio G, et al. Appropriate treatment of invasive candidiasis in ICU: Timing, colonization index, Candida Score & biomarkers, towards de-escalation? Turk J Anaesthesiol Reanim 2016; 44(6):279–82.
17. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 2016;62(4):e1–50.
18. Cornely OA, Sprute R, Bassetti M, et al. Global guideline for the diagnosis and management of candidiasis: An initiative of the ECMM in cooperation with ISHAM and ASM. Lancet Infect Dis 2025;25(5):e280–e293.
19. Bassetti M, Giacobbe DR, Agvald-Ohman C, et al. Invasive fungal diseases in adult patients in intensive care unit (FUNDICU): 2024 consensus definitions from ESGCIP, EFISG, ESICM, ECMM, MSGERC, ISAC, and ISHAM. Intensive Care Med 2024;50(4):502–15.
20. Ferrarese A, Cattelan A, Cillo U, et al. Invasive fungal infection before and after liver transplantation. World J Gastroenterol 2020;26(47):7485–96.
21. Karvellas CJ, Bajaj JS, Kamath PS, et al. AASLD Practice Guidance on acute-on-chronic liver failure and the management of critically ill patients with cirrhosis. Hepatology 2024;79(6):1463–502.
22. Parkins MD, Sabuda DM, Elsayed S, et al. Adequacy of empirical antifungal therapy and effect on outcome among patients with invasive Candida species infections. J Antimicrob Chemother 2007;60(3):613–8.
23. Jyani G, Sharma A, Prinja S, et al. Development of an EQ-5D value set for India using an extended design (DEVINE) study: The Indian 5-level version EQ-5D value set. Value Health 2022;25(7):1218–26.
24. Kollef M, Micek S, Hampton N, et al. Septic shock attributed to Candida infection: Importance of empiric therapy and source control. Clin Infect Dis 2012;54(12):1739–46.
25. Garey KW, Rege M, Pai MP, et al. Time to initiation of fluconazole therapy impacts mortality in patients with Candidemia: A multi-institutional study. Clin Infect Dis 2006;43(1):25–31.
26. Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of candida bloodstream infection until positive blood culture results are obtained: A potential risk factor for hospital mortality. Antimicrob Agents Chemother 2005;49(9):3640–5.
27. Lee W, Liew Y, Chlebicki MP, et al. An observational study on early empiric versus culture-directed antifungal therapy in critically ill with intra-abdominal sepsis. Crit Care Res Pract 2014;2014:479413.
28. Timsit JF, Azoulay E, Schwebel C, et al. Empirical micafungin treatment and survival without invasive fungal infection in adults with ICU-acquired sepsis, candida colonization, and multiple organ failure: The EMPIRICUS randomized clinical trial. JAMA 2016;316(15):1555–64.
29. Pagano L, Caira M, Nosari A, et al. The use and efficacy of empirical versus pre-emptive therapy in the management of fungal infections: The HEMA e-chart project. Haematologica 2011;96(9):1366–70.
30. Cortegiani A, Russotto V, Maggiore A, et al. Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients. Cochrane Database Syst Rev 2016;2016(1):Cd004920.
31. Choudhury A, Kulkarni AV, Arora V, et al. Acute-on-chronic liver failure (ACLF): The "Kyoto Consensus"-steps from Asia. Hepatol Int 2025; 19(1):1–69.
32. Salmanton-García J, Reinhold I, Prattes J, et al. Questioning the 14-day dogma in candidemia treatment duration. Mycoses 2024;67(1): e13672.
33. Bassetti M, Peghin M, Carnelutti A, et al. Clinical characteristics and predictors of mortality in cirrhotic patients with Candidemia and intra-abdominal candidiasis: A multicenter study. Intensive Care Med 2017; 43(4):509–18.