



Original Article

Invasive aspergillosis is a critical determinant of mortality in cirrhosis: a systematic review with meta-analysis

Nipun Verma^{1,*}, Shreya Singh², Arshi Syal³, Pranita Pradhan⁴,
Manvi Singh⁴ and Meenu Singh⁴

¹Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh, 160012, India, ²Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh, 160012, India, ³Department of Internal Medicine, Government Medical College and Hospital, Chandigarh, 160032, India and ⁴Department of Pediatrics, Indian Council of Medical Research Center for Evidence-Based Child Health, Postgraduate Institute of Medical Education and Research, Chandigarh, 160012, India

*To whom correspondence should be addressed. Nipun Verma, MBBS, MD, DM, Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh, 160012, India. Tel: 0172-2754777; E-mail: nipun29j@gmail.com

Increased Mortality with IA in cirrhosis

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Abstract

Invasive fungal infections pose a severe threat in unconventional immunocompromised hosts such as cirrhosis. Herein we review the impact of invasive aspergillosis (IA) on the prognosis of cirrhosis patients. An electronic search for full-text articles describing IA in cirrhosis was conducted and the disease outcomes and mortality (point-estimate and comparative risk) were pooled on random-effects meta-analysis. Of 4127 articles, 11 studies (9 with good/fair and 2 with poor quality) were included. IA was associated with high disease severity and multi-organ failures in cirrhosis. The pooled-mortality of IA was 81.8% (95% CI: 64.3–91.8, $I^2 = 59%$, $P < 0.01$). Estimate's-heterogeneity (I^2) was explored through sub-groups, meta-regression, and influential diagnostics. Mortality estimates were higher among subgroups of acute-on-chronic liver failure (ACLF, 86.4%) and intensive care unit (ICU)-admitted patients (84.0%). The odds of mortality related to IA were 8.9 times higher than controls and much higher in ACLF (OR: 22.5) and ICU-admitted patients (OR: 36.4). The odds of mortality in IA were 4.1, 12.9, and 48.6 times higher than bacterial, no-fungal infections, and no-infection controls. There was no asymmetry in mortality estimates or odds ratios and mortality in IA was high irrespective of country of origin, site of infection, proven or probable category, and quality of study. Thus, IA is associated with very high mortality in cirrhosis patients, especially in ACLF and ICU-admitted patients. Intensive research is needed for the rapid diagnosis and treatment of IA in cirrhosis.

Lay summary

We report a high mortality rate of 81.8% in patients with liver cirrhosis and invasive aspergillosis. Higher odds (8.9 times) of death, especially in patients with ACLF or ICU admission were seen. Mortality was not affected by the country of study, site of infection, proven or probable nature of infection category, and quality of study.

Key words: cirrhosis, invasive aspergillosis, mortality, systematic review, meta analysis.

Introduction

Cirrhosis is a state of immune dysfunction resulting from a multifactorial process comprising increased intestinal perme-

ability, continuous stimulation of immune cells, complement deficiencies, depressed monocytes, neutrophil, and other immune cell functions, all of which predispose to infections.¹ Multi-

ple hospitalizations, antibiotic abuse, and procedures predispose environmental pathogens to gain entry in cirrhosis patients, which are not cleared effectively by the immune system. Fungal infections (FIs) are being increasingly reported in such individuals, and among these, *Aspergillus* species have emerged as critical life-threatening pathogens.² We recently demonstrated an increasing prevalence of invasive aspergillosis (IA) over the last decade among cirrhosis in-patients in a global epidemiological review of FIs. IA in general medical patients has a high case fatality rate ranging from 30.2 to 99% depending on underlying patient condition and system involvement.^{3,4}

Cirrhosis of liver is considered a risk factor for IA but the literature on mortality associated with IA in cirrhosis is poorly characterized.⁵ Cirrhosis patients with IA are associated with a more extended ICU stay and higher mortality (71-100%) than patients without IA.⁶⁻⁸ In addition to the severity of underlying conditions, the lack of prompt diagnosis contributes to the high mortality in cirrhosis patients with IA.⁸ Identification of the factors affecting mortality of IA in cirrhosis may help in recognition of patients requiring more aggressive therapies and thus improve their clinical outcomes. Overall, studies in general medical patients with IA have found an association of higher mortality with old age, bone marrow transplant, rheumatologic conditions, higher sequential organ failure assessment score, use of mechanical ventilation, need for renal replacement therapy, disseminated diseases, elevated serum galactomannan levels.^{9,10} Although less frequent use of high-dose glucocorticoids, less advanced stage of cirrhosis, earlier diagnosis of IA, and well tolerance of a patient to antifungal therapy may confer a favorable outcome, robust systematic evidence is needed to identify factors affecting mortality in patients with IA who have underlying cirrhosis.¹¹ In this systematic review, we estimated the impact of IA on the disease outcomes in patients with cirrhosis and evaluated the contributory factors.

Methods

Study design

The protocol of this systematic review was registered in PROSPERO (CRD42019142782), and it was conducted according to the PRISMA guidelines.¹² The population studied was adults (>18 years) with cirrhosis, context/exposure was IA-infection, comparator(s)/controls were cirrhosis patients without IA (when available), and the outcome was mortality rate.

Literature search

The criteria for study selection were set and reviewed by three independent investigators. An electronic search was conducted in PubMed, Embase, Medline via Ovid, and Web of Science to identify full-text articles describing IA in cirrhosis patients. For studies published in the English language up to 15 January 2021. The search strategy was performed using Boolean combinations

of the MeSH terms of keywords shown in Supplementary Table 1. An independent librarian conducted the searches. The list of references in all original articles and systematic reviews published were manually searched for any additional studies missed on electronic search.

Studies fulfilling all the following criteria were included: (a) Cross-sectional studies, cohort studies, case-control studies. (b) Studies including adults (>18 years) admitted with a diagnosis of cirrhosis. The definition of cirrhosis and acute-on-chronic liver failure (ACLF) was as per the guidelines.¹³ Alcoholic hepatitis was defined as per the American Association for Study of Liver Diseases (AASLD) criteria¹⁴ (c) Studies describing IA in patients with cirrhosis. Definitions for IA were as per the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy, and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group criteria¹⁵ and/or *AspICU* algorithm¹⁶ and (d) Studies with available data on the mortality among cases with IA.

Studies conducted in pediatric intensive care setups (Age <18 years) and duplicate publications, lack of sufficient data, e.g., conference proceedings, poster presentation and meeting abstracts, case reports, etc., were excluded.

Data extraction

The data were independently extracted by three reviewers using a pre-piloted data extraction sheet. For each study, the author name, country of origin, year of conduct, publication, recruitment, design, number of patients with IA, mortality (proportion who died among IA-cases), age, gender, underlying disease severity, co-morbidities, organ failures, details of antifungal therapy, length of stay, were noted. Any difference between the extracted data was settled after discussion with an arbitrator. We used the Newcastle-Ottawa Scale (NOS) to assess the quality of the included studies.¹⁷ The scale enables the assessment of three components, namely study selection (score/star 0 to 4), comparability (score 0 to 2), and outcome (0 to 3) quality.

Statistical analysis

The proportion (%), mean (\pm standard deviation), or median (range) were described as appropriate. Estimates (proportions) of mortality were logit-transformed, pooled, and retransformed to proportions during meta-analysis with a continuity correction of 0.1 for cells with zero value during random effect meta-analysis using REML (restricted maximum likelihood) method.¹⁸ Likewise, estimates of odds ratio (OR) were pooled on REML method. The heterogeneity in estimates was assessed by Tau², I², and chi-square test (Q-statistic). The cutoffs for small, medium and large heterogeneity (I²) were >25%, 50%, and 75%, respectively.¹⁹ We used a pre-defined list of study-level moderators

Table 1. Details of the studies included in the present systematic review and meta-analysis.

Serial number	Study ID	Country, period of conduct	Study design, direction	Number with IA, proven/probable, site of FI	Age [SD], male-%, etiology of cirrhosis (number of patients)	Severity scores (number of patients)	Antifungal received (number of patients) mortality (numbers)	Organ failures (numbers)	Length of hospital stay-in days
1	Lahmer 2019 (7)	Germany, (2016-2018)	Cohort, retrospective	12, probable, pulmonary (12)	59 [8], 75%; ALD: 9, Viral: 1, Others: 2	CTP-A/B/C: 0/0/12, MELD: 31 (8), APACHE-II 26 (8), SOFA 14 (4)	Vori (1), LAMB (11), M: 12/12	Respiratory: 12/12; renal 11/12	16 (7)
2	Levesque 2019 (6)	France, (2005-2015)	Cohort, retrospective	17, Proven + Probable, pulmonary (15), pulmonary and cerebral (2)	56 [14.5], 88%, ALD: 8, viral: 7, other: 2	CTP: 11.8 (3.1), MELD: 23.2 (13.3), SOFA: 13.4 (8.5)	Vori (1), Caspo (5), LAMB: (2) M: 12/17	Cerebral 9/17, respiratory 12/17, liver 4/17, renal 7/17, CVS 12/17	NA
3	Gao 2018 (21)	China, (2011-2016)	Cohort, retrospective	20, probable; pulmonary (20)	42 [11]; 90%;	MELD: 25.6 (6.2), MELD Na: 27.2 (33.0), CLIF-C ACLFs: 45.8 (19.0)	Vori (8), M: 11/20	Cerebral 3/20, respiratory 3/20, liver 19/20, renal 2/20, coagulation 11/20	NA
4	Prattes 2017 (11)	Austria, (2013-2015)	Single-arm cohort, prospective	2, Probable, pulmonary (2)	55 [0.7], 100%; ALD: 1/2, PBC/PSC:1/2	CTP- A/B/C:11/0, MELD: 15.5 (14-17)	Vori (2), M: 0/2	NA	35 (7-63)
5	Lahmer 2014 (22)	Germany, (2010-2012)	Single-arm cohort, retrospective	5, Proven, fungemia (5)	NA	NA	Antifungal NOS (5), M: 5/5	NA	NA
6	Chen 2014 (23)	China, (2008-2012)	Single-arm cohort, retrospective	19, proven + probable, pulmonary (19)	54 [11.3], 63%, ALD: 3, viral:11, AIH:1, other: 4	CTP: 11 (2) child B (6), child C (13), MELD: 22 (7)	Caspo (6), vori (6), Itra (1), LAMB (1), none (5), M: 17/19	Renal: 4/19	NA
7	Hassan 2014 (24)	Egypt, (2013-2013)	Three arm cohort, prospective	5, proven, SFP (2), fungemia (3)	58.2 [8.0], 60%	CTP: 12.6 (1.5), MELD: 29 (8.1)	NA, M: 1/5	NA	NA
8	Gustor 2014 (25)	Belgium, (2006-2012)	Cohort, Prospective	15, proven (6), probable (8), pulmonary (11), brain abscess (2), disseminated with cerebral involvement (2)	48 [17.7], 80%, ALD-AH: 15	CTP: 12 (8-14), MELD: 27 (19-40)	Caspo (4), LAMB (2), Vori (2), Caspo fb LAMB (2), Vori + LAMB (1), M: 14/15	Respiratory 8/15, Renal 8/15, CVS 10/15	NA

Table 1. Continued.

Serial number	Study ID	Country, period of conduct	Study design, direction	Number with IA, proven/probable, site of FI	Age [SD], male-%, etiology of cirrhosis (number of patients)	Severity scores (number of patients)	Antifungal received (number of patients) mortality (numbers)	Organ failures (numbers)	Length of hospital stay-in days
9	Chen 2013 (26)	China, (2008-2012)	Cohort, retrospective	39, probable, pulmonary (39)	43 [11.6], 74.3%; viral: 37, AIH: 2	NA	Capso (10), vori (9), Itra (7), no (13), M: 37/39	NA	NA
10	Lin 2013 (27)	China, (2006-2009)	Cohort, retrospective	1, Proven, fungemia (1)	NA, HBV (1)	NA	M: 1/1	NA	NA
11	Wu 2012 (28)	China, (2007-2010)	Single arm cohort, retrospective	29, proven and probable; pulmonary (29)	47.4 [11.2], 82.7%; viral-HBV: 29/29	NA	M: 25/29	Renal: 16/29	NA

FI fungal infection, SD standard deviation, ALD alcoholic liver disease. CTP Child-Turcotte-Pugh, MELD Model for End-Stage Liver Disease, Na- Sodium, APACHE Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) score, SOFA Sequential Organ Failure Assessment, CLIF chronic liver failure score, ACLF acute on chronic liver failure, PBC/PSC primary biliary cholangitis/sclerosing cholangitis, NAFLD Non-alcoholic fatty liver disease, AIH Autoimmune hepatitis, SFP spontaneous fungal peritonitis, mDF Maddrey discriminant function, ABIC Age, serum Bilirubin, INR, and serum Creatinine score, CVS cardio vascular system, CSF cerebrospinal fluid, GIT gastro intestinal tract, M: Mortality, hep hepatitis, NA not available, Caspo: Caspofungin, Vori: Voriconazole, Itra: Itraconazole, LAMB: Liposomal Amphotericin B.

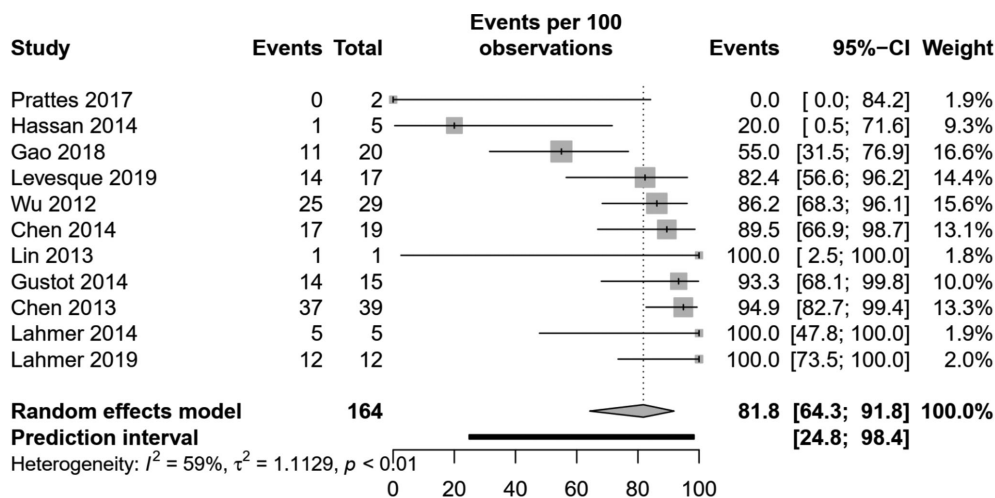


Figure 1. Forest – plot showing the pooled mortality in patients of cirrhosis with invasive aspergillosis. The mortality in the included studies is represented by the grey square with horizontal bars indicating the 95% confidence interval. The diamond at the end denotes the overall pooled mortality.

to explore heterogeneity in estimates on sub-groups and meta-regression. These included population-attributes (all-cirrhosis or ACLF, ICU-admission or all-hospitalized patients, mean-MELD-cases), exposure-attributes (site of infection, category of IFI), study-attributes (continent, country, income status, year of conduct, decade, design), and quality score of study.

Outlier and influential study assessments were performed to identify studies distorting the pooled estimates.²⁰ Leave one study out plots were made for sensitivity analysis. Funnel plot and Eggers regression were done to assess the asymmetry in estimates, respectively. All analysis was performed using the R studio v. 1.2.5033, and a p-value of < 0.1 was considered significant for heterogeneity and < 0.05 for sub-groups and meta-regression.

Results

The search yielded a total of 4127 articles, of which 11 studies (162 patients) were included in the review.^{6,7,11,21–27,28} The search strategy and PRISMA flowchart is shown in Supplementary Table 1 and Supplementary Figure 1, respectively. The characteristics of included studies are illustrated in Table 1. The studies originated from China (5 studies),^{21,23,26–28} Germany (2 studies),^{7,22} Belgium (1 study),²⁵ Austria (1 study),¹¹ France (1 study)⁶ and Egypt (1 study).²⁴ Studies included patients with ACLF (6 studies)^{6,7,11,21,23,26,28} or cirrhosis of any severity (5 studies)^{6,7,11,23,24} with admission in ICU (5 studies) or hospital area not specified (6 studies).^{6,7,22,24,26} Seven studies examined pulmonary-aspergillosis,^{6,7,11,21,23,26,28} and one study²⁷ examined fungemia, while three studies examined multiple sites of infection.^{22,24,25} IA was attributable to proven-IFI in 3 studies,^{22,24,27} probable in 4 studies^{7,11,21,27} or proven + probable-IFI (4 studies).^{6,23,25,28} Mycological characteristics were poorly reported in these studies. The severity of IA patients across studies was MELD: 26.4 (range: 15.5–38.0), compared to 22.8

(range: 15.0–26.1) among controls without IA. One-thirty-seven patients died out of 164 patients with IA. Antifungal use was reported in 6 studies, of which all patients received antifungals in 4 studies^{7,22,26,28} and 76% in one study⁶ and 66% in one study.²⁵ Data were insufficient to discern the impact of antifungal use on the mortality of IA patients in the studies.

Meta-analysis: The pooled mortality in cirrhosis patients with IA was 81.8% (95% CI: 64.3–91.8) (Figure 1). The I^2 value (53%) indicated medium heterogeneity, i.e., variation in the context of point estimates. There was no statistically significant difference in the mortality estimates in any subgroup (Table 2). But the estimates were numerically high in studies reporting ACLF patients (86.4%, 95% CI: 65.5–95.5) and ICU patients (84.0%, 95% CI: 41.9–97.6). Meta-regression for potential effect-modifiers and MELD-score cases showed non-significance and concurred with sub-group analysis (Supplementary Table 2).

Outlier assessment: A study by Hassan et al.²⁴ was identified as an outlier with studentized residual > 2.0 (Supplementary Figure 2). Leave one study out plot showed a pooled estimate of 85.3% (95% CI: 71.8–92.9, I^2 : 51%, $P = 0.03$) after removing this study (Supplementary Figure 3).

Sensitivity analysis: We pooled mortality of IA patients from studies ($n = 6$) with sample size ≥ 15 to address variation in estimates due to small sample size [85.0% (95% CI: 70.7–93.0), I^2 : 66%, $P = 0.01$].

Asymmetry in estimates: The funnel plot (Supplementary Figure 4) indicated no asymmetry, small study effect, or publication bias in mortality estimates of IA in cirrhosis (Eggers-test: $z = 0.2463$, $P = 0.8055$).

Quality assessment: The included studies were of good (4 studies), fair quality (5 studies), or poor quality (2 studies) (Supplementary Table 4). However, the estimates did not vary with regard to the quality scores of studies (Table 2).

Table 2. Pooled mortality of invasive aspergillosis in various study level subgroups.

Sub group (number of studies)	Cases	Mortality (%)	95% CI	Heterogeneity (I^2)	Sub-group difference (P-value)
Admission status					0.83
All-hospitalized (n = 6)	86	80.7	59.2–92.3	57%	
ICU only (n = 5)	78	84.3	41.9–97.6	66%	
Patient population					0.41
ACLF (n = 6)	109	86.4	65.5–95.5	65%	
All-cirrhosis (n = 5)	55	71.7	29.3–93.9	61%	
Quality of study					0.14
NOS score 4 (n = 2)	48	87.4	74.7–94.2	0%	
NOS score 5 (n = 1)	5	98.1	8.9–100.0	NA	
NOS score 6 (n = 2)	51	95.3	83.5–98.8	0%	
NOS score 7 (n = 3)	39	65.7	35.0–87.2	53%	
NOS score 8 (n = 3)	21	71.7	10.6–98.2	72%	
IFI category					0.73
Probable (n = 4)	73	79.9	28.7–97.5	77%	
Proven (n = 3)	11	64.9	4.9–98.5	40%	
Proven + probable (n = 4)	80	87.0	77.4–92.9	0%	
Number of sites involved					0.82
Single (n = 8)	139	83.5	67.4–92.5	57%	
Multiple (n = 3)	25	77.3	11.9–98.8	75%	
Examined IFI					0.95
Pulmonary (n = 7)	138	83.3	66.7–92.5	63%	
Multiple sites (n = 3)	25	77.3	11.9–98.8	75%	
Fungemia (n = 1)	1	91.7	1.7–100.0	NA	
Continent of study					0.15
Africa (n = 1)	5	20.0	2.7–69.1	NA	
Asia (n = 5)	108	84.5	63.7–94.5	70%	
Europe (n = 5)	51	86.4	69.7–94.6	9%	
Income of country where study was conducted*					0.03
High (n = 5)	51	86.4	69.7–94.6	9%	
Upper middle (n = 5)	108	84.5	63.7–94.5	70%	
Lower middle (n = 1)	5	20.0	2.7–69.1	NA	
Decade of study conduct					0.66
Before 2010 (n = 2)	30	86.4	69.1–94.7	0%	
After 2010 (n = 9)	134	80.7	57.3–92.8	66%	
Direction of study					0.32
Prospective (n = 3)	22	50.0	3.5–96.5	76%	
Retrospective (n = 8)	142	85.2	70.2–93.4	53%	

* Classification bases on the World bank data (2020), CI: Confidence Interval, ICU: Intensive Care Unit, ACLF: Acute-on-Chronic Liver Failure, NOS: New Castle Ottawa Scale, NA: Not Available.

Comparative risk of mortality with IA in cirrhosis

The OR of mortality was higher (8.9, 95% CI: 3.5–22.6) in cases with IA compared to those without IA (Figure 2). The I^2 indicated low heterogeneity (18%) in OR estimates. The odds of mortality in IA cases were highest among ACLF (OR: 22.5, 95% CI: 1.9–26.1) and ICU-admitted patients (OR: 36.4, 95% CI: 3.2–413.2). Further, such odds (Supplementary Figure 5) were higher when cases with IA were compared to controls with bacterial infection (OR: 4.1), no-fungal

infection (OR: 12.9), and no-infection (OR: 48.5). As there was a varying proportion of bacterial infections among controls, which could modify the comparative risk estimates, we adjusted the pooled-OR for these proportions (adjusted OR: 9.3, 95% CI: 3.8–22.6).

On an exploratory analysis with limited power, there was a trend towards a decline in the odds of mortality in cirrhosis patients with IA over time. This trend was confirmed on meta-regression with the year of conduct as a predictor of odds

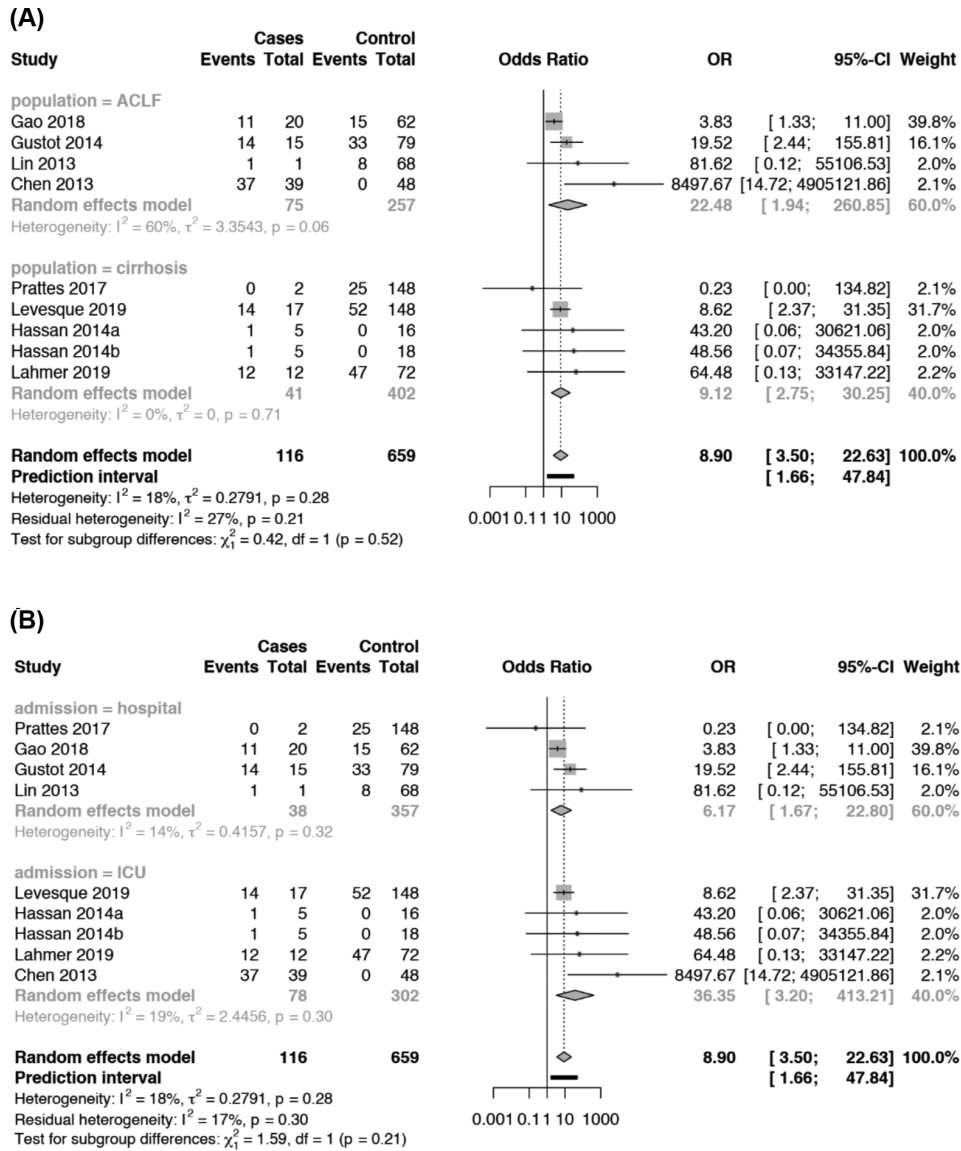


Figure 2. Forest- plot showing Odds Ratio of mortality among cirrhosis patients with invasive aspergillosis (IA) compared to patients without IA by sub-groups (A) Population-all-cirrhosis or ACLF (B) Admission status- hospital area not specified or intensive care unit (ICU). The OR in the included studies is represented by the grey square with horizontal bars indicating the 95% confidence interval. The diamond at the end denotes the overall pooled estimate.

ratio (beta-coefficient: -0.477 , 95% CI: -0.949 to -0.004 , $P = 0.048$). (Figure 3).

There was no asymmetry in the OR estimates indicating no publication bias or small study effects (Eggers-test: $z = 0.929$, $P = 0.105$) (Supplementary Figure 6). Two outlier studies^{6,21} were identified for OR-estimates (Supplementary Figure 7), and leave one study out plots showed a higher estimate after removing these studies (OR: 13.7–13.8) (Supplementary Figure 8).

Discussion

This systematic review synthesized a pooled estimate of 82% mortality in cirrhosis patients with IA. 9 times higher odds of death was identified in cirrhosis patients with IA than

controls. The pooled mortality (84–86%) and comparative risk estimates (22–36 times) were numerically highest among studies performed in ACLF or ICU-admitted patients. There was no influence of various parameters such as country of origin, study design, patient profile, year of research on the mortality estimates. A trend of decline in the odds of mortality associated with IA was noted in cirrhotics over time.

Infections are associated with multi-organ failures and high mortality in cirrhosis.²⁹ Early treatment of complications and optimum critical care with organ support is a key to improve survival in cirrhosis patients with infections.³⁰ However, it is crucial to understand which infections impact the outcomes and to what degree. Hence, the resources may be directed, and strategies may be prioritized to alleviate poor outcomes in infected

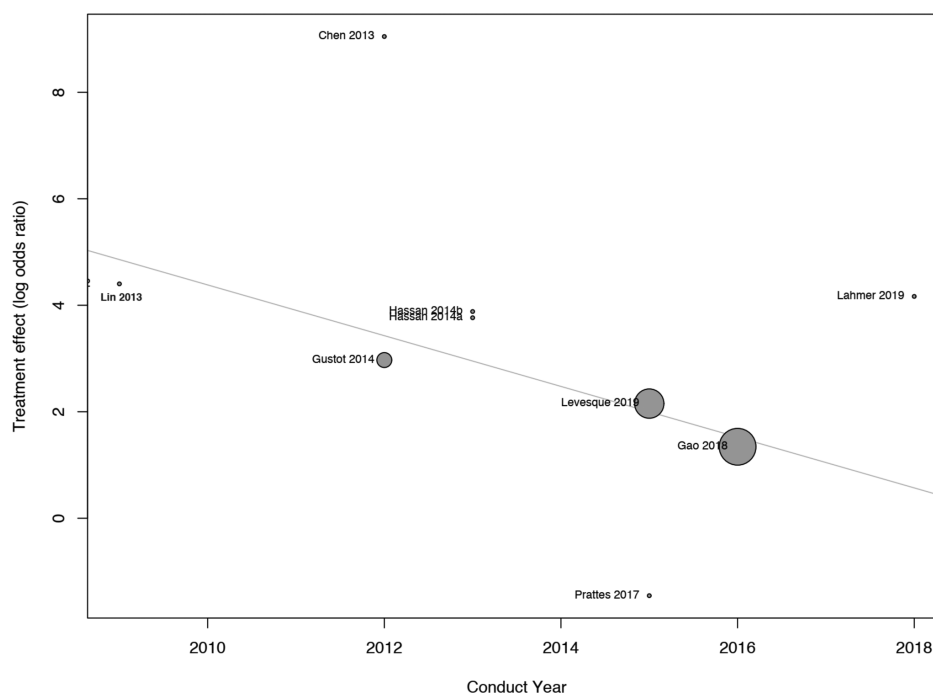


Figure 3. Graphical representation of meta-regression depicting a declining trend in odds ratios of mortality due to IA in cirrhosis patients over time.

patients. Fungal infections are increasingly recognized for deterioration, organ failures, death, and transplant delisting in cirrhosis.³⁰ This systematic review has demonstrated IA as a significant reason for high mortality (>80%) in cirrhosis patients among fungal infections.

Fungal infections traditionally affect patients with malignancy and immunodeficiency states. However, certain fungal infections, such as IA, can affect unconventional hosts like cirrhosis.^{5,16} This is possibly due to cirrhosis-associated immune dysfunction (CAID), where both innate and adaptive immune arms are defective.¹ Neutrophil, monocyte, dendritic cell functions are impaired, phagocytosis is defective, and oxidative burst is dysregulated and hence unable to clear the pathogens and damage associated products effectively.¹ This enhances the susceptibility to a host of bacterial and fungal infections in cirrhosis. Further, platelets have been shown to inhibit the growth of *Aspergillus* spp. *in vitro*, and thrombocytopenia in cirrhosis can also contribute to a higher susceptibility of patients to *Aspergillus* infections.²⁹ CAID is shown to worsen with disease progression in cirrhosis.¹ A state of systemic inflammation with immunoparesis sets in during ACLF, which predisposes to multi-drug resistant bacterial and fungal infections, which often culminate in mortality.¹ Likely because of this, this study also showed higher estimates of mortality in ACLF and ICU patients.

In general, the crude mortality due to the IA ranges from 30.2 to 99% in critically ill patients varying according to underlying disease, site of infection, and antifungal management.^{3,30} In patients with cirrhosis and fungal infections, the mortality is high due to associated organ failures. We showed that IA, in

particular, is associated with very high mortality, which is > 10 times higher than those without IA. A delayed diagnosis of IA and inappropriate treatment may contribute to such high mortality in cirrhosis. The diagnosis of IA in cirrhotic patients is often delayed due to a low index of suspicion and non-specific clinical/radiological signs coupled with a limited yield of fungal cultures and biomarkers.⁵ Unfortunately, this delay is inevitable as lung biopsy or bronchoscopy is challenging in cirrhotics due to coagulopathy and the poor health of these patients. Delayed antifungals, wrong choice of medication like fluconazole for IA, and inadequate dosing of appropriate drugs add further to the poor outcomes. In this review, we couldn't discern the effect of antifungals on the patient's outcomes due to the scarcity of data.

Interestingly, a reduction in the comparative risk of mortality was noted over the last decade in the present study. However, a similar decrease in the pooled mortality estimates was not seen, suggesting a possible rise in mortality in the comparator groups. Rising mortality in controls could be because of an increased rate of hospitalizations of more severe cirrhosis over time or mortality due to multi-drug resistant bacterial infections or unknown factors. It is further supported by a global study that demonstrated up to 70% mortality in multi-resistant bacterial infections. Investigating the reasons for this temporal change in estimates will be an interesting future perspective. A limitation of this analysis is the few studies with limited power for subgroup analysis. The probable cases were more than the proven cases in this review, but interestingly the probable cases had numerically higher mortality estimates (80%) than proven cases (65%). This

could be due to better tolerability of proven IA patients to withstand invasive diagnostic tests and better prognosis. However, the proven cases in this review were SFP and fungemia, both of which are diagnosed with less invasive tests such as ascitic tap and venous blood sampling, respectively. Conversely, probable IA cases were all due to pulmonary aspergillosis, which suggest a need for early diagnosis and treatment of such patients.

To conclude, IA in patients with cirrhosis is associated with high mortality, especially in ACLF or ICU admitted patients. Large prospective multi-centric studies can improve our understanding of the factors affecting outcomes in these patients. Efforts to extend the available diagnostic armamentarium, derivation and validation of prediction rules for diagnosis and prognosis of IA in these patients, and prompt therapeutic intervention with new antifungals are needed to improve the management of cirrhotic patients with IA.

Supplementary material

Supplementary material is available at [MMYCOL](https://www.mycologyjournal.com) online.

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Disclosure statement

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

References

- Albillos A, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. *J Hepatol*. 2014;61:1385–1396.
- Alexopoulou A, Vasilieva L, Agiasotelli D, Dourakis SP. 2015. Fungal infections in patients with cirrhosis. *J Hepatol*. 2015;63:1043–1045.
- Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. *Clin Infect Dis*. 2001;32:358–366.
- Sun KS, Tsai CF, Chen SCC, Huang WC. Clinical outcome and prognostic factors associated with invasive pulmonary aspergillosis: an 11-year follow-up report from Taiwan. *PLoS One*. 2017;12:e0186422.
- 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;39:503–513.
- Levesque E, Ait-Ammar N, Dudau D et al. 2019. Invasive pulmonary aspergillosis in cirrhotic patients: analysis of a 10-year clinical experience. *Ann Intensive Care*. 2019;9:31.
- Lahmer T, Brandl A, Rasch S et al. Prevalence and outcome of invasive pulmonary aspergillosis in critically ill patients with liver cirrhosis: an observational study. *Sci Rep*. 2019;9:1–8.
- Falcone M, Massetti AP, Russo A, Vullo V, Venditti M. Invasive aspergillosis in patients with liver disease. *Med Mycol*. 2011;49:406–413.
- Taccone FS, Van den Abeele AM et al. Epidemiology of invasive aspergillosis in critically ill patients: clinical presentation, underlying conditions, and outcomes. *Crit Care*. 2015;19:7.
- Rotjanapan P, Chen YC, Chakrabarti A et al. Epidemiology and clinical characteristics of invasive mould infections: a multicenter, retrospective analysis in five Asian countries. *Med Mycol*. 2018;56:186–196.
- Prattes J, Hoening M, Krause R et al. Invasive aspergillosis in patients with underlying liver cirrhosis: a prospective cohort study. *Med Mycol*. 2017;55:803–812.
- Liberati A, Altman DG, Tetzlaff J et al. The PRISMA Statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6:e1000100.
- Angeli P, Bernardi M, Villanueva C et al. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol*. 2018;69:406–460.
- Crabb DW, Im GY, Szabo G, Mellinger JL, Lucey MR. Diagnosis and treatment of alcohol-associated liver diseases: 2019 practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2020;71:306–333.
- Donnelly JP, Chen SC, Kauffman CA et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. *Clin Infect Dis*. 2020;71:1367–1376.
- Blot SI, Taccone FS, Van Den Abeele AM et al. A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. *Am J Respir Crit Care Med*. 2012;186:56–64.
- Wells G, Shea B, O'Connell D et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed on 30-Feb-2021.
- Jackson D, Bowden J, Baker R. How does the DerSimonian and Laird procedure for random effects meta-analysis compare with its more efficient but harder to compute counterparts? *J Stat Plan Inference*. 2010;140:961–970.
- Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
- Viechtbauer W, Cheung MW-L. Outlier and influence diagnostics for meta-analysis. *Res Synth Methods*. 2010;1:112–125.
- Gao J, Zhang Q, Wu Y et al. Improving survival of acute-on-chronic liver failure patients complicated with invasive pulmonary aspergillosis. *Sci Rep*. 2018;8:876.
- Lahmer T, Messer M, Schwerdtfeger C et al. Invasive mycosis in medical intensive care unit patients with severe alcoholic hepatitis. *Mycopathologia*. 2014;177:193–197.
- Chen J, Yang Q, Huang J, Li L. Clinical findings in 19 cases of invasive pulmonary aspergillosis with liver cirrhosis. *Multidiscip Respir Med*. 2014;9:1.
- Hassan EA, El-Rehim ASA, Hassany SM, Ahmed AO, Elsherbiny NM, Mohammed MH. Fungal infection in patients with end-stage liver disease: low frequency or low index of suspicion. *Int J Infect Dis*. 2014;23:69–74.
- Gustot T, Maillart E, Bocci M et al. Invasive aspergillosis in patients with severe alcoholic hepatitis. *J Hepatol*. 2014;60:267–274.
- Chen J, Yang Q, Huang J, Li L. Risk factors for invasive pulmonary aspergillosis and hospital mortality in acute-on-chronic liver failure patients: a retrospective-cohort study. *Int J Med Sci*. 2013;10:1625–1631.
- Lin LN, Zhu Y, Bin Che F, Gu JL, Chen JH. Invasive fungal infections secondary to acute-on-chronic liver failure: a retrospective study. *Mycoses*. 2013;56:429–433.
- Wu Z, Ling Z, Shao F, Sheng J, Li L. Invasive pulmonary aspergillosis in patients with acute-on-chronic liver failure. *J Int Med Res*. 2012;40:1958–1965.
- Perkhofer S, Kehrel BE, Dierich MP et al. Human platelets attenuate Aspergillus species via granule-dependent mechanisms. *J Infect Dis*. 2008;198:1243–1246.
- Piano S, Singh V, Caraceni P et al. Epidemiology and effects of bacterial infections in patients with cirrhosis worldwide. *Gastroenterology*. 2019;156:1368–1380.e10.