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REVIEW ARTICLE

Global epidemiological burden of fungal infections in cirrhosis patients: A systematic review with meta-analysis

Nipun Verma[1] | Shreya Singh[2] | Manvi Singh[3] | Anil Chauhan[3] | Pranita Pradhan[3] | Nishant Jaiswal[3] | Arunaloke Chakrabarti[2] | Meenu Singh[3]

[1]Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

[2]Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

[3]Indian Council of Medical Research Center for Evidence-Based Child Health, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Correspondence
Meenu Singh, Professor of Pediatrics, Chief of Pediatric Pulmonology, Head of SAARC Telemedicine Network and Telemedicine Centre, Co Chair of Cochrane India Network, Head of ICMR Advanced Centre for Evidence based Child Health, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh, 160012.
Email: meenusingh4@gmail.com

Nipun Verma, Assistant Professor, Department of Hepatology, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh. Phone: +911722754777.
Email: nipun29j@gmail.com

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Abstract

Background and Aims: Fungal infections (FIs) have serious implications, yet understated in cirrhosis. Therefore, we reviewed the epidemiology and trends of FIs among cirrhotics.

Methods: Four electronic databases were searched for full-text articles describing prevalence of FIs in cirrhosis. Studies from post-transplant, malignancy and classical-immuno-deficiency patients were excluded. A random-effects meta-analysis was done to pool estimates of FIs (overall, and by type and infection-site), and their variation(I^2) was explored on moderator-analysis and meta-regression. Risk of bias and asymmetry in estimates was assessed by a checklist and Egger's regression, respectively.(CRD42019142782).

Results: Thirty-four low-risk and four moderate-risk studies (31 984 cirrhotics) were included. Pooled estimates of overall FIs (17 studies), invasive fungal infections (IFIs; 17 studies), invasive candidiasis (23 studies) and invasive aspergillosis (16 studies) in cirrhosis were 10.2%(6.0-16.9), 9.5%(5.4-16.2), 4.0%(2.0-8.0) and 2.8%(1.5-5.3), respectively (I^2 > 90%;each). Site of FIs in decreasing order of pooled prevalence was pulmonary, urinary tract, bloodstream, peritoneal, oesophageal and cerebral. Geographic differences in these estimates were remarkable, with highest burden of overall FIs from Belgium, the United States and India. Non-albicans-*Candida* and *Aspergillus* infections have increased over the last decade in cirrhosis. Intensive-care-unit (ICU)-admitted and acute-on-chronic liver failure (ACLF) patients had the highest prevalence of IFIs. MELD score(cases), bias score and sample size across studies were the predictors of variance in overall FI estimates. Diabetes, steroid and broad-spectrum antibiotic-exposure, and multiple organ failures were the common predispositions reported in patients with FIs.

Conclusions: FIs impose a substantial burden in cirrhosis. ACLF and ICU admission should be considered as a host factor for defining IFIs. Epidemiology of FIs can guide interpretation of biomarkers and antifungal treatment in cirrhosis.

KEYWORDS
ACLF, invasive fungal infections, liver failure, mortality, mycoses

Nipun Verma and Meenu Singh are Joint senior authors

1 | INTRODUCTION

Fungi are ubiquitous, opportunistic pathogens, affecting billions of patients globally, of which 150 million are critically ill, and 1.5 million die annually.[1] Despite an enormous burden, fungal infections (FIs) are often under-recognised, poorly reported and mistreated worldwide.[1] Moreover, without robust national and international surveillance systems, the precise estimation of FIs in in-patients remains a challenge.

Cirrhosis, a terminal stage in any chronic liver injury, imposes a considerable health burden of 10.6 million admissions and 1.32 million deaths annually.[2] Immune dysfunction, gastrointestinal dysbiosis, barrier disruption, frequent hospitalisations, invasive procedures, malnutrition and exposure to broad-spectrum antibiotics invite many bacterial and FIs in cirrhosis.[3] Although bacterial infections are extensively described in cirrhosis, the literature on FIs is poorly characterised. Only two brief systematic reviews demonstrate mortality and nosocomial origin of spontaneous fungal peritonitis (SFP) in cirrhosis patients.[4,5] Few studies have reported higher mortality (60%–100%) in cirrhosis patients with FIs compared with non-infected and bacterially infected cirrhosis patients[6] that outnumber mortality estimates from FIs in non-neutropenic patients (30%–40%).[1] Recently, aspergillosis has been associated with very high mortality (81.8%) in cirrhosis patients.[7] Invasive fungal infections (IFIs) have been shown to cause multi-organ failures, acute-on-chronic liver failure (ACLF) and transplant de-listings in cirrhosis patients.[8,9] Despite profound implications, FIs are sometimes disregarded in cirrhosis as a disease of the minority. Physicians would make appropriate decisions with a better understanding of the regional and global epidemiology of FIs in cirrhosis. The diagnosis of FIs can be strengthened with knowledge of the pre-test probability of FIs and the use of fungal biomarkers in cirrhosis. The recent EORTC/MSG guidelines[10] on IFIs advocate using biomarkers and an empiric approach to antifungals in non-neutropenic septic patients with a high probability of IFIs, which is poorly known in cirrhosis patients at present. Appropriate resources may be channelled in areas with a high prevalence of FIs in cirrhosis. Therefore, this systematic review was conducted to inform the global epidemiology of FIs in cirrhosis. We reported the prevalence of FIs and factors determining their variation in cirrhosis. Further, as the incidence of FIs is perhaps changing during the COVID-19 pandemic, this review will serve as an estimate of FIs in cirrhosis during the pre-COVID era.[11]

Keypoints

- The true epidemiology of fungal infections (FIs) in cirrhosis is unknown.
- We systematically reviewed the literature on FIs in cirrhosis.
- Pooled prevalence of overall FIs from 17 studies among cirrhosis was 10.2% (95 CI: 6.0-16.9).
- Candida followed by Aspergillus was the commonest pathogen causing FIs.
- Lungs followed by the urinary tract were the commonest site of FIs.
- Patients with FIs had high disease severity scores and multi-organ failures.
- Geographic variations were high in the estimates of FIs.
- Non-Albicans Candida and Aspergillus infections have increased over the last decade in cirrhosis.
- ICU-admitted and ACLF patients had the highest burden of FIs and may be considered host factors for defining IFIs.
- Fungal infections are diverse, and merit targeted evaluation and treatment in cirrhosis

2 | METHODS

We followed the PRISMA guidelines[12] in the study, and the protocol was registered at PROSPERO (CRD42019142782). A librarian (PP) used a pre-defined search strategy including cirrhosis and fungal infections related keywords (Table S1, S2) to search PubMed, Ovid, Web of Science and EMBASE until 31 March 2020. The bibliography of studies, review articles and grey literature were then searched for additional articles.

2.1 | Study selection

Full-text observational studies (any language) describing the prevalence of FIs in cirrhosis were included. Studies in patients with haematological malignancies, solid organ or stem cell transplantation, classical immune-deficiency, and those on chemotherapy were excluded. Editorials, letters, case reports, reviews, abstracts and posters were excluded for insufficient methodology. The patient population was cirrhosis, intervention/exposure was any type or site of FI, and the outcome was the prevalence of FIs. After removing duplicates, screening titles and abstracts, the articles were evaluated for inclusion, followed by a full-text review. Data screening and extraction were done on pre-piloted data extraction sheets independently by NV, SS, MS and AC and validated by NV. An arbitrator (MeS) resolved the discrepancies. The authors of the studies were contacted for details when required.

2.2 | Data extraction and definitions

Variables extracted were author's name, publication year, the period of conduct, country, design, recruitment strategy, population, admission status, sample attributes, exposure attributes, FI case attributes, prevalence estimates and limitations of the study. Cirrhosis, its aetiology and ACLF were defined as per standard guidelines (Table S3).[8,13-15] Alcoholic hepatitis was determined by clinical and/or histological criteria.[16] FIs were defined by the modified-EORTC/MSG criteria,[17] Asp-ICU criteria[18] or positive

fungal culture (Table S3). Fungal culture positivity from non-sterile sites in the absence of other substantiating evidence of infection was considered colonisation or possible IFIs and was excluded from the analysis.

Overall FIs were defined as a composite group comprising any type or site of FI, including IFIs (proven+probable/putative or proven), superficial FIs and site-specific FIs. Invasive candidiasis (IC) and invasive aspergillosis (IA) were reported as described in modified-EORTC/MSG criteria.[17] Sites of IFIs were as follows: pulmonary IFI, urinary tract infection, cerebral IFI, SFP and fungemia according to isolation/description of fungus from respective sites. Fungal bloodstream infection without any identifiable source was considered fungemia, and when it was secondary, the identified focus was considered the site of FI.

2.3 | Data synthesis

Proportions (%), mean (standard deviation) or median (range) were described for the appropriate data. The risk of bias in studies was assessed independently by NV and SS using a checklist for prevalence studies[19] and detailed in Table S4. Discrepancies were resolved by an arbitrator (MeS).

The prevalence was calculated as the proportion of patients affected by the given FI divided by the study population. Prevalence estimates were logit-transformed[20] during meta-analysis and pooled using fixed, and random-effects models with DerSimonian and Laird (DL) method[21] and interpreted as per the random-effects model. The variance in prevalence estimates was assessed by Tau^2, I^2 and chi-square test (Q-statistic). I^2 of >25%, >50% and >75% represented low, medium and large variance.[22] Reasons for the observed variance were explored on subgroup analyses (using mixed or random-effects model with DL method), meta-regression (mixed-effects model), metaplots (to visualise the impact of moderators), and outliers assessment using studentised residuals and cooks distances of individual studies.[23]

A defined set of study-level moderators were examined to explore variance, including population attributes (age, sample size, disease severity scores: CTP, MELD, ACLF or all-cirrhosis, infection status, admission area), exposure attributes (number or type of FI examined, criteria of FIs, age and disease severity of cases), study attributes (continent, country, income status, climate, year of publication or conduct, recruitment strategy and sampling design) and risk of bias score. Leave one study out plot was generated for sensitivity analysis. Funnel plot and Egger's regression were performed to assess asymmetry in the context of prevalence estimates.[24] R-studio v.1.2.5033 was used to perform the analysis. The p-value of <0.05 and <0.10 was considered significant for statistical tests and variance evaluation.

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as the research in this article is related to review of existing literature.

3 | RESULTS

Of 4127 articles searched, 38 studies[6,25-61] were included in the review (Figure 1). The excluded articles and reasons are detailed in Figure 1 and Table S5. The characteristics of the included studies (31 984 patients) are detailed in Table 1 and S6-S7. No study reported FIs in cirrhosis out-patients. Seventeen studies examined for multiple FIs; 21 studies examined specific FIs (pulmonary IFI, SFP, etc). The studies emanated from the Europe (n = 18),[26,28,33,35-37,39,41-43,45,47-49,51,53,59,60] Asia (n = 10),[27,30-32,38,44,52,54,56,57] North America (n = 7)[6,25,29,34,46,55,58] or Africa (n = 2),[40,50] and one was a global study.[61]

3.1 | Sample attributes

The denominator among the studies was all-cirrhosis (any aetiology or severity) in 28 studies[6,25-27,29,33,34,37-48,50,51,53-55,58-61] or ACLF in 10 studies.[28,30-32,35,36,49,52,56,57] The included patients were admitted in ICU (11 studies)[28,32,33,37,40,41,43,55,56,59,60] or in the hospital (area not specified; 27 studies).[6,25-27,29-31,34-36,38,39,42,44-54,57,58,61] The sample population (31 984 patients) had a median age of 56 years (range: 39-63), and 60% were males (range: 57-89). The criteria for cirrhosis was the histopathology with or without clinico-radiological features (10 studies), ICD coding (2 studies), clinical-biochemical-radiological or endoscopic features (4 studies) APASL-ACLF (3 studies), EASL-ACLF (2 studies), Chinese society definition (2 studies), and not clear in 15 studies. The aetiology of cirrhosis was heterogenous. Alcohol, viral or non-alcoholic fatty liver disease was the commonest causes of cirrhosis. Severity of cirrhosis in the sample population (from 30 studies) was described with a median Child-Turcotte-Pugh score of 11 (range: 9-13), Child-Pugh class-C in 43%–84% and median MELD score of 22.0 (range: 16-34).

3.2 | Description of fis

Of 31 984 patients (38 studies),[6,29,30,32-36,38-44,47-50,52-54,56-61] 1627 had overall FIs and 1581 had IFIs (proven+probable). Proven IFIs were reported in 1118 out of 21 230 patients (29 studies).[6,26-29,31,33,35-37,39-46,48-56,58,60] IC was reported in 847 out of 16 070 patients (23 studies),[6,25,26,28,29,31,33,35,36,39-41,43,45,46,48,49,51-56] IA in 189 out of 12 577 patients (16 studies)[25,28,30-32,36,38,40,41,47,49,55-57,59,60] and cryptococcosis in 3 out of 147 patients (2 studies).[25,31] The sites of FIs were pulmonary (18 studies; 238/12792 patients),[6,25,28-32,35,36,38,41,47,49,52,56,57,59,60] urinary tract (7 studies; 93/2800 patients),[6,29,31,41,49,52,56] fungemia (15 studies; 321/15334 patients),[6,28,29,31,33,35-37,39-41,43,49,52,56] peritonitis (19 studies; 93/14172 patients),[6,26,27,31,33,35,39,40,42-46,49-51,53,54,56] cerebral (3 studies; 6/1206 patients)[31,36,60] and oesophageal (3 studies; 19/1523 patients).[6,29,56]

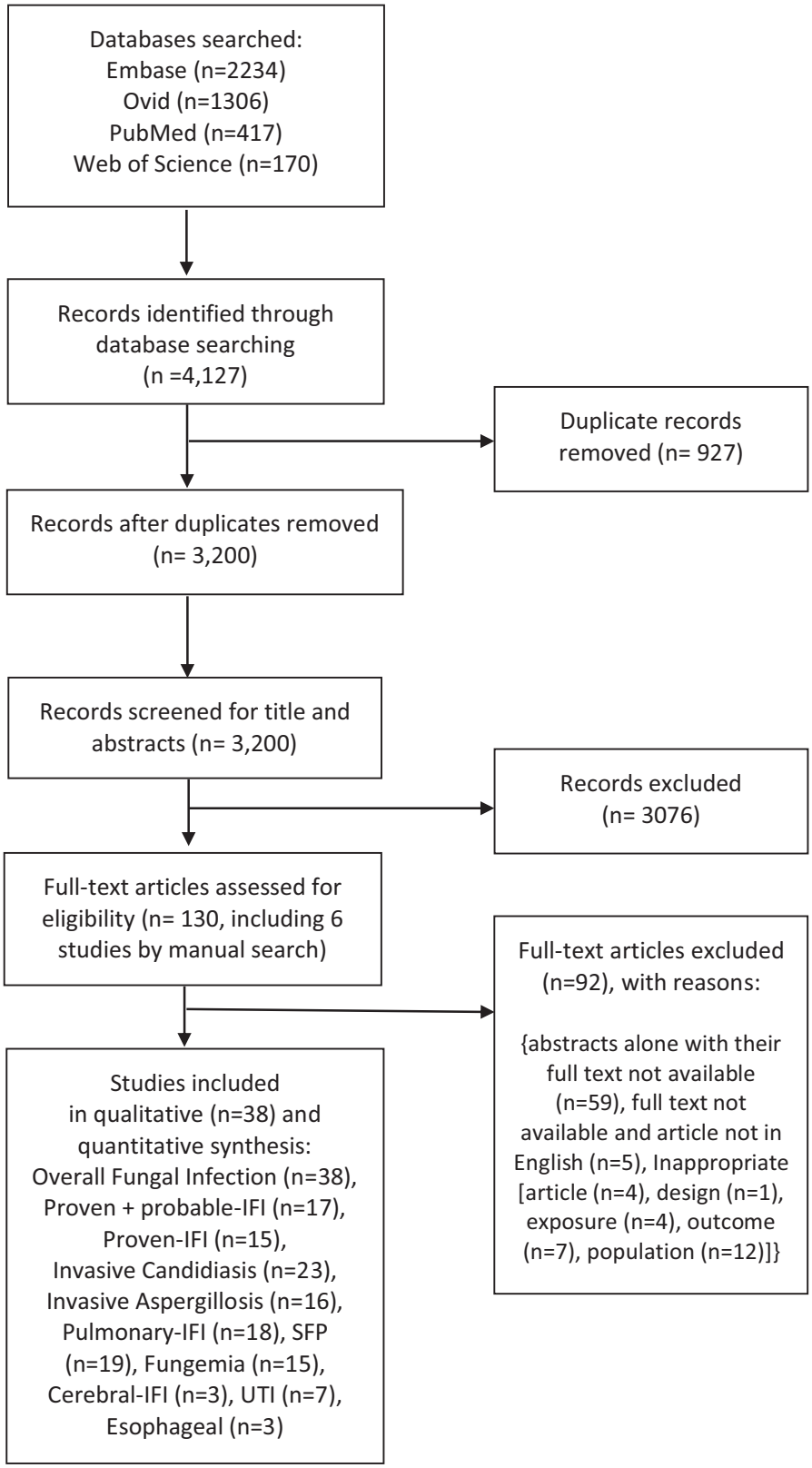

FIGURE 1 PRISMA flow diagram

3.3 | Case attributes

Patients with FIs had poor liver functions, with a median MELD score of 27.0; range: 15.5-38.0, and multi-organ failures. FIs were predominantly nosocomial (range: 70%–100% cases). The most prevalent symptoms were fever (range: 90%–100%), cough with expectoration (range: 22%–100%) and haemoptysis (5.8%–69%) among patients with pulmonary aspergillosis. Patients with IFIs commonly had ascites (range: 43%–97%), refractory ascites (42%–44%) and hepatic encephalopathy (range: 14%–40%) with a hospital stay ranging from

TABLE 1 Characteristics of the studies in the systematic review

Study-ID	Country, period of conduct	Study design, direction and recruitment	FI evaluated and criteria	Prevalence of FI	Site, mode of infection	Site-specific organism	Mycological characteristics
Population: Hospitalised cirrhosis							
Mabee 1998[25]	USA, 1992-1994	Longitudinal, retrospective, convenient	Multiple FI, culture positive	Overall: 7/21, proven+probable: 7/21, proven: 0/21	Pulmonary (n = 7), NC: 100%	Pulmonary (IA:2, IC: 3, Cryptococcus:1, Torulopsis glabrata:1)	*Aspergillus fumigatus* (n = *2*), *Candida* spp. (n = *3*), *Cryptococcus neoformans* (n = *1*), *Torulopsis glabrata* (n = *1*)
Bajaj 2012[29]	USA, 2010-2011	Longitudinal, prospective, consecutive	Multiple FI, culture positive	Overall: 14/207, proven+probable: 9/207, proven: 1/207	UTI (n = 7), SSTI (n = 2), pulmonary (n = 1), fungemia (n = 1), oesophageal (n = 3), NC: 100%	UTI, SSTI, pulmonary, fungemia, oesophageal (all IC:14)	*Candida* spp. (n = *14*)
Bajaj 2014[34]	USA, NS	Longitudinal, prospective, consecutive	Multiple FI, culture positive	Overall: 89/507, proven+probable: 89/507, proven: NS	NS	NS	NS
Piano 2017[48]	Italy, 2011-2016	Longitudinal, prospective, consecutive	Multiple FI, culture positive	Overall: 14/317, proven+probable: 14/317, proven: 14/317	NS	NS	*Candida* spp. (n = *14*)
El-Amin 2017[50]	Egypt, NS	Cross-sectional, retrospective, convenient	Multiple FI, culture positive	Overall: 6/100, proven+probable: 3/100, proven: 3/100	SFP (n = 3), SSTI (n = 1), Oral (n = 1), GIT (n = 1), NS	NS	NS
Bajaj 2017[6]	USA, NS	Longitudinal, prospective, consecutive	Multiple FI, culture positive	Overall: 134/1052, proven+probable: 96/1052, proven: 24/1052, total patients: infected+non-infected: 2743	UTI (n = 57), SSTI (n = 16), pulmonary (n = 15), fungemia (n = 16), oesophageal (n = 14), SFP (n = 8), oropharyngeal (n = 8), NC: 100%	NS	*Candida spp.* (n = *104*, *C albicans: 58*, *C non-albicans: 46*), *other* (n = *30*)
Bajaj 2019[58]	USA, 2013-2017	Longitudinal, retrospective, consecutive	Multiple FI, culture positive	Overall: 67/998, proven+probable: 67/998, proven: 67/998	NS, NC: 86.6%, CA: 13.4%	NS	NS
Piano 2019[61]	Global, 2015-2016	Longitudinal, prospective, consecutive	Multiple FI, culture positive, CDC	Overall: 57/1570, proven+probable: 57/1570, proven: NS	NS	NS	NS

(Continues)

TABLE 1 (Continued)

Study-ID	Country, period of conduct	Study design, direction and recruitment	FI evaluated and criteria	Prevalence of FI	Site, mode of infection	Site-specific organism	Mycological characteristics
Bartoletti 2014[39]	Italy, 2008-2012	Longitudinal, retrospective, consecutive	Fungemia, culture positive	Overall: 16/8874, proven+probable: 16/8874, proven: 16/8874	Fungemia (n = 13), SFP (n = 3), NS	Fungemia (IC:13), SFP (IC:3)	*Candida spp.* (n = *16*, *C albicans 14*, *C parasilosis 1*, *C glabrata 1)*
Chen 2014[38]	China, 2008-2012	Longitudinal, retrospective, consecutive	Pulmonary IFI, EORTC/MSG	Overall: 19/6600, proven+probable: 19/6600, proven: NS	Pulmonary (n = 19), NS	Pulmonary (IA:19)	*Aspergillus* spp. (n = *19)*
Prattes 2017[47]	Austria, 2013-2015	Longitudinal, prospective, consecutive	Pulmonary IFI, EORTC/MSG	Overall: 2/150, proven+probable: 2/150, proven: 0/150	Pulmonary (n = 2), NC:100%	Pulmonary (IA:2)	*Aspergillus* spp. (n = *2)*
Bert 2003[26]	France, 1998-1999	Longitudinal, retrospective, consecutive	SFP, culture positive	Overall:1/72, proven+probable: 1/72, proven: 1/72	SFP (n = 1), CA: 100%	SFP (IC:1)	*Candida* spp. (n = *1*, *C albicans 1)*
Cheong 2009[27]	S. Korea, 2000-2007	Longitudinal, retrospective, consecutive	SFP, culture positive	Overall: 3/236, proven+probable IFI: 3/236 proven: 3/236	SFP (n = 3), NC:100%	SFP (NS)	NS
Piroth 2014[42]	France, 2010-2011	Longitudinal, prospective, consecutive	SFP, culture positive	Overall: 7/190, proven+probable: 7/190, proven: 7/190	SFP (n = 7), NC:71.4%, CA: 28.6%	NS	NS
Li 2015[44]	China, 2011-2013	Cross-sectional, retrospective, consecutive	SFP, culture positive	Overall: 9/288, proven+probable: 9/288, proven: 9/288	SFP (n = 9), NC:77.8%, CA: 22.2%	NS	NS
Friedrich 2015[45]	Germany, 2007-2013	Longitudinal, retrospective, consecutive	SFP, culture positive	Overall: 10/311, proven+probable: 10/311, proven: 10/311	SFP (n = 10), NC: 80%, CA: 20%	SFP (IC:10)	*Candida* spp.(n = *10)*
Karvellas 2015[46]	Canada, 1996-2011	Longitudinal, retrospective, consecutive	SFP, culture positive	Overall: 11/126, proven+probable: 11/126, proven: 11/126	SFP (n = 11), NC: 100%	SFP (IC: 11)	*Candida* spp. (n = *11*, *C albicans: 9*, *C glabrata: 1*, *C tropicalis: 1)*
Gravito-Solares 2017[51]	Portugal, 2006-2015	Case-control, retrospective, consecutive	SFP, culture positive	Overall: 8/231, proven+probable: 8/231, proven: 8/231	SFP (n = 8), NC: 25%, CA: 75%	SFP (IC:1, Other:1)	*Candida* spp. (n = *7*, *C albicans: 3*, *C krusei: 2*, *C Lusitaniae: 1*, *C tropicalis: 1)*, *Geotrichum capitatus* (n = *1)*
Lutz 2017[53]	Germany, 2012-2016	Longitudinal, prospective, consecutive	SFP, culture positive	Overall: 1/86, proven+probable: 1/86, proven: 1/86	SFP (n = 1), NC: 100%	SFP (IC:1)	*Candida* spp. (n = *1*, *C albicans: 1)*

TABLE 1 (Continued)

Study-ID	Country, period of conduct	Study design, direction and recruitment	FI evaluated and criteria	Prevalence of FI	Site, mode of infection	Site-specific organism	Mycological characteristics
Shi 2017[54]	China, 2014-2014	Longitudinal, retrospective, consecutive	SFP, culture positive	Overall: 2/575, proven+probable: 2/575, proven: 2/575	SFP (n = 2), NC: 100%	SFP (IC:2)	*Candida* spp. (n = *2*, *C glabrata: 2)*
Population: Hospitalised ACLF							
Lin 2013[31]	China, 2006-2009	Case-control, retrospective, consecutive	Multiple FI, EORTC/MSG	Overall: 60/126, proven+probable: 60/126, proven: 14/126	Fungemia (n = 10), SFP (n = 2), Cerebral (n = 2), UTI (n = 17), Pulmonary (n = 15), GIT (n = 14), NS	Fungemia (IC:9, IA:1), SFP (IC:2), cerebral (cryptococcal:2)	*Candida* spp. (n = *11*, *C albicans: 9*, *C tropicalis: 1*, *C glabrata: 1)*, *Aspergillus spp.* (n = *1)*, *Cryptococcus neoformans* (n = *2)*
Fernandez 2017[49]	Spain, NS	Longitudinal, retrospective, convenient	Multiple FI, EORTC/MSG	Overall: 17/642, proven+probable: 17/642, proven: 7/642	Fungemia (n = 5), SFP (n = 2), Pulmonary (n = 1), UTI (n = 1), unknown (n = 8), NC:75%, CA: 25%	Fungemia (IC:5), SFP (IC:2), Pulmonary (IA:1), UTI (IC:1)	*Candida* spp. (n = *7)*, *Aspergillus spp.* (n = *1)*
Cai 2017[52]	China, 2008-2014	Longitudinal, retrospective, consecutive	Multiple FI, culture positive	Overall: 30/389, proven+probable: 30/389, proven: 10/389	Pulmonary (n = 19), UTI (n = 1), Fungemia (n = 1), unknown (n = 9), NC: 23.8%, HCA: 66.6%, CA: 9.5%	Pulmonary (IC:18, Trochosporon phullans:1), UTI (IC:1), Fungemia (IC:1)	*Candida* spp. (n = *20) and Trichosporon pullulans* (n = *1)*, *unknown* (n = *9)*
Verma 2018[56]	India, 2016-2016: 12months	Longitudinal, retrospective, consecutive	Multiple FI, EORTC/MSG	Overall: 39/264, proven+probable: 39/264, proven: 11/264	Pulmonary (n = 13), UTI (n = 7), SFP (n = 6), UTI and pulmonary (n = 6), fungemia (n = 5), UTI and oesophageal (n = 2), NC:100%	NS	*Candia* spp. (n = *25)*, *Aspergillus spp.* (n = *14)*
Karvellas 2010[28]	UK, 2003-2005	Longitudinal, retrospective, consecutive	Fungemia, culture positive	Overall: 8/184, proven+probable IFI: 8/184 proven: 7/184	Fungemia (n = 7), pulmonary (n = 1), NC:100%	Fungemia (IC:7), pulmonary (IA:1)	*Candida* spp. (n = *7)*, *Aspergillus spp.* (n = *1)*
Wernlund 2014[35]	Denmark, 2009-2011	Longitudinal, retrospective, convenient	Fungemia, culture positive	Overall: 3/51, proven+probable: 3/51 proven: 3/51	Fungemia (n = 1), pulmonary (n = 1), SFP (n = 1), NS	Fungemia (IC:1), pulmonary (IC:1), SFP (IC:1)	*Candida* spp. (n = *3; C glabrata: 1*, *C dublinienses: 1 and C albicans: 1)*
Wu 2012[30]	Wu 2012, China, 2007-2010	Longitudinal, retrospective, consecutive	Pulmonary IFI, AspICU, EORTC/MSG	Overall: 29/470, proven+probable:29/470, proven: NS	Pulmonary (n = 29), NS	Pulmonary (IA:29)	NS

(Continues)

TABLE 1 (Continued)

Study-ID	Country, period of conduct	Study design, direction and recruitment	FI evaluated and criteria	Prevalence of FI	Site, mode of infection	Site-specific organism	Mycological characteristics
Chen 2013[32]	China, 2008-2012	Longitudinal, retrospective, consecutive	Pulmonary IFI, EORTC/MSG	Overall: 39/787, proven+probable: 39/787, proven: NS	Pulmonary (n = 39), NS	Pulmonary (IA:39)	*Aspergillus* spp. (n = *39*)
Gustot 2014[36]	Belgium, 2006-2012	Longitudinal, prospective, consecutive	Pulmonary IFI, AspICU, EORTC/MSG	Overall: 25/94, proven+probable: 25/94 proven: 16/94	Pulmonary (n = 19), cerebral (n = 2), disseminated (n = 2), fungemia (n = 2), NC:100%	Pulmonary (IA:11, PCP:8), cerebral (IA:2), dissemited (IA:2), fungemia (IC:2)	*Aspergillosis* (n = *15*), *Candidiasis* (n = *2*; *C glabrata: 2*), *Pneumocystis jiroveci* (n = *8*)
Gao 2018[57]	China, 2011-2016	Longitudinal, retrospective, consecutive	Pulmonary IFI, EORTC/MSG	Overall: 20/565, proven+probable: 20/565, proven: 0/265	Pulmonary (n = 20), NC: mostly	Pulmonary (IA:20)	*Aspergillus* spp. (n = *14*, *A fumigatus: 13*, *A flavus: 1*)
Population: ICU-admitted cirrhosis							
Lahmer 2014b[33]	Germany, 2010-2012	Case-control, retrospective, consecutive	Multiple FI, CDC and EORTC/MSG	Overall: 15/120, proven+probable: 15/120, proven: 15/120	Fungemia (n = 10), SFP (n = 5), NS	Fungemia, SFP (IC:15)	*Candida* spp. (n = *15*)
Hassan 2014[40]	Egypt, 2013-2013: 6months	Longitudinal, prospective, convenient	Multiple FI, culture positive	Overall: 12/46, proven+probable: 12/46, proven: 12/46	Fungemia (n = 5), SFP (n = 7), NS	Fungemia (IC:2, IA:3), SFP (IC:5, IA:2)	*Candida* spp. (n = *4*, *C albicans: 4*), *Apergillus* spp. (n = *5*, *A niger: 4*, *A flavus: 1*), *PCR positive* (n = *3*)
Lahmer 2014a[41]	Germany, 2010-2012	Longitudinal, retrospective, convenient	Multiple FI, culture positive	Overall: 8/120, proven+probable:8/120, proven: 8/120	Fungemia (n = 3), pulmonary (n = 4), UTI (n = 1), NS	Primary fungemia (IA:2, IC:1), pulmonary (IA:1, IC:3), UTI (IC:1)	*Candidia* spp. (n = *3*, *C albicans: 3*, *C glabrata: 1*, *C krusei: 1*, *C parasilosis: 1*), *Aspergillus spp.* (n = *5*, *A Fumigatus: 5*, *A nidulans: 1*)
Theocharidou 2016[43]	UK, 2009-2011	Longitudinal, prospective, consecutive	Multiple FI, EORTC/MSG	Overall: 8/782, proven+probable:8/782, proven: 8/782	Fungemia (n = 4), SFP (n = 4), NC:100%	NS	*Candida* spp. (n = *8*, *C albicans: 5*, *C glabrata: 2*, *C parasilosis: 1*)
Lan 2018[55]	USA, 2001-2012	Longitudinal, retrospective, convenient	Multiple FI, culture positive	Overall: 570/1438, proven+probable: 570/1438, proven: 570/1438	NS	NS	*Yeast* (n = *487*), *Candida albicans* (n = *70*), *Aspergillus* spp. (n = *13*)
Galbois 2014[37]	France, 1998-2010	Longitudinal, retrospective, consecutive	Fungemia, blood culture	Overall: 238/2383, proven+probable: 238/2383, proven: 238/2383	Fungemia (n = 238), NS	Fungemia (NS)	NS

TABLE 1 (Continued)

Study-ID	Country, period of conduct	Study design, direction and recruitment	FI evaluated and criteria	Prevalence of FI	Site, mode of infection	Site-specific organism	Mycological characteristics
Lahmer 2019[59]	Germany, 2016-2018	Case-control, retrospective, consecutive	Pulmonary IFI, EORTC/MSG	Overall: 12/84, proven+probable: 12/84, proven: NS	Pulmonary (n = 12), NC: 100%	Pulmonary (IA:12)	*Aspergillus* spp. (n = *10*)
Levesque 2019[60]	France, 2005-2015	Longitudinal, retrospective, consecutive	Pulmonary IFI, AspICU	Overall: 17/986, proven+probable: 17/986, proven: 2/986	Pulmonary (n = 15), cerebral and pulmonary (n = 2), NC:100%	Pulmonary (IA:15), cerebral (IA:2)	*Aspergillus* spp. (n = *17, A fumigatus: 15, A flavus*: 2)

Note: FI: fungal infection, IFI: invasive fungal infection, USA: United States of America, NC: nosocomial, CA: community acquired, IA: invasive aspergillosis, IC: invasive candidiasis, UTI: urinary tract infection, SSTI: skin and soft tissue infection, SFP: spontaneous fungal peritonitis, GIT: gastrointestinal tract, IPA: invasive pulmonary aspergillosis, ICU: intensive care unit, EORTC/MSG: European Organization for Research and Treatment of Cancer Mycoses study group criteria, NS: not stated

10 to 36 days. Common predisposing factors for FIs in cirrhosis were diabetes, more than one antibiotic use, steroid exposure, steroid non-response, prior bacterial infection, SBP prophylaxis, high hepatitis B virus-DNA, mechanical ventilation, cerebral failure and haemodialysis (Table S6).

3.4 | Mycological characteristics according to site

Aetiology of pulmonary IFI (14 studies; 189 cases) was aspergillosis (n = 152), candidiasis (n = 26), pneumocytosis (n = 8), torulopsis (n = 1), trichosporonosis (n = 1) and cryptococcosis (n = 1). Aetiology of UTI (7 studies; 27 cases) was candidiasis in all patients. Aetiology of fungemia (11 studies; 58 patients) was candidiasis (n = 52) and aspergillosis (n = 6). Aetiology of SFP (12 studies; 53 cases) was candidiasis (n = 50), aspergillosis (n = 2) and *Geotrichum* infection (n = 1). Aetiology of cerebral IFI (3 studies; 6 patients) was aspergillosis (n = 4) and cryptococcosis (n = 2).

3.5 | Fungal species distribution

Genus and species of fungi were reported in 29 and 17 studies, respectively (Table 1). Among *Candida* isolates (n = 246) in cirrhosis, the majority were *C albicans* (n = 178); however, non-albicans *Candida* species (NAC) isolation have dramatically increased over the last decade (8.0% to 41.1%; $P = .010$) (Table S8). NACs comprised 36%, 31% and 26% of *Candida* isolates from Europe, Asia and North America (Table S9). Among the *Aspergillus* species (n = 44), *A fumigatus* (n = 35), followed by *A flavus* (n = 4), *A niger* (n = 4) and *A nidulans* (n = 1) were reported (Table S8). Over the past decade, *Aspergillus* constituted 21.4% of all fungal isolates in cirrhosis (Table S8-S9). Other fungi isolated were *Cryptococcus neoformans* (n = 3), *Torulopsis glabrata* (n = 1), *Pneumocystis jiroveci* (n = 8), and *Geotrichum capitus* (n = 1), and rare FIs like mucormycosis, histoplasmosis, etc, were poorly represented.

3.6 | Meta-analysis with subgroup analysis

3.6.1 | *Overall FI*

The pooled % prevalence of overall FIs in cirrhosis from 38 studies that examined both single and multiple FIs was 5.3 (95% CI: 3.4-8.0). It was higher 10.2 (95% CI: 6.0-16.9) when 17 studies that examined multiple FIs were pooled (Figure S1). On subgroup analysis, the main reasons for variation in overall FI estimates were population studied, geographic distribution, economic status of the country and the study's decade of conduct (Table 2). Studies with ACLF or ICU-admitted patients in the denominator had higher overall FI estimates than all-hospitalised patients (8.6%, 9.0% and 3.2%, respectively; $P = .02$) (Figure 2A). The highest pooled prevalence was seen in studies from Belgium (26.6%), the United States (16.1%) and India

(14.8%) ($P < .01$) (Figure 3A). Estimates from lower-middle-income countries (14.1%) were higher than upper-middle (3.7%) and high-income countries (5.3), $P < .01$ (Table 2). Reduction in pooled estimates of overall FIs was seen over the past decade, that is 9.0% (95% CI: 4.1-18.6) to 4.4% (95% CI: 2.9-6.8), $P < .01$ (Figure S2).

IFIs (proven+probable): The pooled % prevalence of IFIs in cirrhosis (17 studies that examined multiple FIs) was 9.5 (95% CI: 5.4-16.2; I^2: 98%; $P < .01$). The critical reasons for variation in IFI's estimates were population studied, the geographic distribution of study, and the study's decade of conduct (Table S10). Studies with ACLF (14.4%) and ICU-admitted patients (10.8%), as denominators, reported a higher prevalence of IFIs than all-hospitalised patients (6.4%), $P = .05$ (Figure 2A). The pooled estimate of IFIs was highest in Asian studies (19.1%) ($P = .01$). Country-level variations were high (Figure 3B), with the highest estimates from Belgium (26.6%) and China (21.6%). Estimates from upper-middle (21.6%) and lower-middle (12.4%) income countries were higher than high-income countries ($P < .01$) (Table S10). A reduction in IFIs prevalence was noted over the past decade (42.5 to 7.5%, $P < .01$) (Table S10).

3.6.2 | *Proven IFI*

The pooled % prevalence of proven IFI in cirrhosis (15 studies that examined multiple FIs) was 5.9 (95% CI: 2.7-12.4, I^2:98%; $P < .01$). Studies with ICU-admitted (10.8%) and ACLF patients (6.8%) in the denominator had a higher prevalence of proven IFI than all-hospitalised patients (3.5%), $P = .04$ (Table S11). Continent/Country-wise estimates of proven IFI in cirrhosis were remarkable. Reduction proven IFI was noted in cirrhosis over the past decade ($P = .01$).

3.6.3 | *Invasive candidiasis*

The pooled % prevalence of IC in cirrhosis (23 studies) was 4.0 (95% CI: 2.0-8.0, I^2: 97%; $P < .01$). The main reason for variation in the estimates was geographic differences, population studied and study's decade (Table S12). Studies from Africa, the United States (Figure 3C) and lower-middle-income countries reported high estimates of IC in cirrhosis. Studies with ICU-admitted cirrhosis (8.0%) in the denominator reported higher estimates of IC than all-hospitalised patients (2.9%), $P = .18$ (Figure 2A). The prevalence of IC was numerically lower in the past decade (3.1% vs. 6.8%, $P = .20$).

3.7 | Invasive aspergillosis

The pooled % prevalence of IA in cirrhosis (16 studies) was 2.8 (95% CI: 1.5-5.3; I^2: 94%; $P < .01$). The prime reasons for variation in IA estimates were geographic differences, population studied and study's decade. Geographical, regional, income and climate-wise distribution of IA estimates in cirrhosis are described in (Figure 3D and Table S13). Studies with ICU-admitted (4.0%) or ACLF patients (3.6%) in the denominator reported a numerically higher prevalence of IA than those with all-hospitalised patients (1.5%), $P = .27$ (Figure 2A). A numerically higher prevalence of IA was noted over the past decade in cirrhosis (1.5% to 3.3%, $P = .26$) (Table S13).

3.8 | Sites of FIs

Site-wise pooled prevalence of FIs (Figure 2B) was highest for pulmonary IFI (3.4%) followed by fungal-UTI (2.6%), fungemia (1.9%), SFP (1.7%), EC (1.3%) and cerebral IFI (0.9%). Subgroup analysis (Table S14-S19) revealed that pulmonary IFI prevalence was reported highest in studies from India and Germany, fungal-UTI from the United States and India, fungemia from Egypt, and SFP from Egypt and Canada. In general, the estimates of FIs at various sites were numerically higher from lower-middle-income or tropical countries. Estimates of pulmonary and cerebral IFI were highest among ACLF patients. Estimates of SFP and fungemia were highest in studies from ICU patients, while fungal-UTI estimates were highest in studies from all-clubbed hospitalised cirrhosis patients. A targeted evaluation of the site of infection in a study yielded a more precise estimate of given FI in cirrhosis. Estimates of fungal-UTI, fungemia and SFP were numerically higher in studies with the infected population in the denominator than mixed (infected and non-infected) populations.

3.9 | Variation in estimates as per the study design

The variations in prevalence of fungal infections according to study design: sampling strategy and direction of recruitment were not significant statistically (Table 2 and S10-S17).

3.10 | Risk of bias

Most included studies were at low ROB (34 out of 38 studies) and moderate ROB (4 out of 38 studies) (Table S20). Sensitivity analysis revealed an overall FI prevalence of 4.8% (3.0-7.5) in studies with low ROB, viz-à-vis 11.6% (2.6-38.8) in moderate ROB studies. The variations in prevalence of each FI as per ROB scores are given in Table 2 and S10-S17.

3.11 | Meta-regression to explore the variance in estimates

Studies with smaller sample sizes, ACLF or ICU patients in the denominator, multiple FIs as evaluation target, conducted beyond last decade, and moderate ROB had a higher prevalence of overall FIs (Table S21). Variance in the estimates of IFI, proven IFI, IC, IA, pulmonary IFI, fungal-UTI, fungemia and SFP, respectively, could be explained on meta-regression (Tables S22-29). The significant moderators affecting

TABLE 2 Summary of findings table for prevalence of overall fungal infections in cirrhosis

Pooled prevalence	Overall FIs (%; 95% CI)[§]	Studies, Variance (I^2)	Risk of Bias	P-value (subgroup differences)[†,‡]	Comments
	5.3 (3.4-8.0)	38 studies, 98%	Low (34/38) and moderate (4/38)		Composite diagnosis that includes any type or site of fungal infections
Examined-FI				0.09[†]	
Multiple fungal infections	10.2 (6.0-16.9)	17 studies, 98%	Low (15/17) and moderate (2/17)		Selective inclusion of ACLF patients (n = 5), ICU patients (n = 6), infected sample (n = 7) and convenient sampling (n = 3)
Pulmonary IFI only	3.9 (1.5-9.4)	8 studies, 97%	Low (7/8) and moderate (n = 1)		Selective inclusion of ACLF patients (n = 3), ICU patients (n = 3), infected sample (n = 1) and convenient sampling (n = 1)
SFP only	2.6 (1.5-4.5)	9 studies, 69%	Low (9/9)		Selected sample with SBP in all patients (n = 9)
Fungemia only	2.7 (0.3-20.7)	4 studies, 99%	Low (3/4) and moderate (1/4)		Selective inclusion of ACLF patients (n = 3), ICU patients (n = 3), infected sample (n = 1) and convenient sampling (n = 1)
Population				0.02[†]	
Hospitalised cirrhosis	3.2 (1.8-5.8)	20 studies, 97%	Low (19/20) and moderate (1/20)		Selective evaluation of fungemia (n = 1), pulmonary IFI (n = 3), SFP (n = 9), infected sample (n = 16) and convenient sampling (n = 2)
Hospitalised ACLF	8.6 (4.3-16.4)	10 studies, 97%	Low (8/10) and moderate (2/10)		Selective evaluation of fungemia (n = 2), pulmonary IFI (n = 3) and convenient sampling (n = 2)
ICU-admitted cirrhosis	9.0 (3.6-20.5)	8 studies, 99%	Low (7/8) and moderate (1/8)		Selective evaluation of fungemia (n = 1), pulmonary IFI (n = 2), convenient sampling (n = 1) and infected sample (n = 2)
Continent				<0.01[‡]	
Africa	13.3 (2.8-45.0)	2 studies, 90%	Low (1/2) and moderate (1/2)		Reported proven IFI in ICU patients (n = 2)
North America	14.8 (7.3-27.9)	7 studies, 99%	Low (6/7) and moderate (1/7)		Selective inclusion of infected sample (n = 7)
Asia	3.9 (1.5-10.0)	10 studies, 98%	Low (10/10)		Select evaluation of pulmonary IFI (n = 4), SFP (n = 3), ACLF patients (n = 5) and ICU patients (n = 1)
Europe	3.6 (2.0-6.6)	18 studies, 96%	Low (16/18) and moderate (2/18)		Select evaluation of SFP (n = 5), pulmonary IFI (n = 3), fungemia (n = 3) in ACLF patients (n = 5), ICU patients (n = 4) and infected sample (n = 1)
Global	3.6 (2.8-4.7)	1 study, NA	Low (1/1)		Selective inclusion of infected sample
Economic status				<0.01[‡]	
Lower-middle income	14.1 (7.1-26.2)	3 studies, 80%	Low (2/3) and moderate (1/3)		Selective inclusion of ACLF patients (n = 1), ICU patients (n = 1) and convenient sampling (n = 2)

(Continues)

TABLE 2 (Continued)

Pooled prevalence	Overall FIs (%; 95% CI)[§]	Studies, Variance (I^2)	Risk of Bias	P-value (subgroup differences)[†,‡]	Comments
Upper-middle income	3. 7 (1.1-11.3)	8 studies, 98%	Low risk (8/8)		Selective evaluation of SFP (n = 2), pulmonary IFI (n = 4) and ACLF patients (n = 4)
High income	5.3 (3.2-8.7)	26 studies, 98%	Low (23/26) and moderate (3/26)		Selective evaluation of fungemia (n = 4), pulmonary IFI (n = 4), convenient sampling (n = 3), infected sample (n = 15), ACLF patients (n = 4) and ICU patients (n = 8)
Climate of country				0.76[†]	
Tropical	4.8 (2.0-11.1)	12 studies, 98%	Low (11/12) and moderate (1/12)		Selective evaluation of IPA (n = 4), SFP (n = 3), proven IFI (n = 1), convenient sampling (n = 2), ACLF patients (n = 6) and ICU patients (n = 3)
Temperate	5.6 (3.4-9.2)	25 studies, 98%	Low (22/25) and moderate (3/25)		Selective evaluation of fungemia (n = 4), pulmonary IFI (n = 4), SFP (n = 6), infected sample (n = 14), ACLF patients (n = 5) and ICU patients (n = 6)
Decade of conduct				<0.01[†]	
Past one	4.4 (2.9-6.8)	28 studies, 97%	Low (25/28) and moderate (3/28)		Selective evaluation of fungemia (n = 2), pulmonary IFI (n = 7), SFP (n = 4), proven IFI (n = 3), infected sample (n = 10), convenient sampling (n = 4), ACLF patients (n = 10) and ICU patients (n = 6)
More than past one	9.0 (4.1-18.6)	10 studies, 99%	Low (9/10) and moderate (1/10)		Selective evaluation of fungemia (n = 2), SFP (n = 5), pulmonary IFI (n = 1), convenient sampling (n = 1), infected sample (n = 6), ACLF patients (n = 2) and ICU patients (n = 2)
Recruitment				0.26[†]	
Convenient	10.2 (3.2-28.2)	5 studies, 93%	Moderate (4/5) and low (1/5)		Selective evaluation of fungemia (n = 1), pulmonary IFI (n = 1), infected sample (n = 1), ACLF patients (n = 2), ICU patients (n = 1) and proven IFI (n = 1)
Consecutive	4.8 (3.0-7.5)	33 studies, 98%	Low (33/33)		Selective evaluation of fungemia (n = 3), pulmonary IFI (n = 7), SFP (n = 9), proven IFI (n = 2), infected sample (n = 17), ACLF patients (n = 10) and ICU patients (n = 8)
Direction				0.58[†]	
Retrospective	4.9 (2.8-8.6)	27 studies, 99%	Low (24/27) and moderate (3/27)		Selective evaluation of fungemia (n = 4), SFP (n = 7), pulmonary IFI (n = 7), convenient sampling (n = 4), infected sample (n = 11), ACLF patients (n = 9) and ICU patients (n = 9)

TABLE 2 (Continued)

Pooled prevalence	Overall FIs (%; 95% CI)[§]	Studies, Variance (I^2)	Risk of Bias	P-value (subgroup differences)[†,‡]	Comments
Prospective	6.6 (3.8-11.2)	11 studies, 97%	Low (10/11) and moderate (1/11)		Selective evaluation of SFP (n = 2), pulmonary IFI (n = 1), convenient sampling (n = 1), infected sample (n = 7), ACLF patients (n = 1) and ICU patients (n = 2)
Infected population in denominator				0.79[†]	
Infected patients	5.7 (3.3-9.7)	18 studies, 98%	Low (17/18) and moderate (1/18)		Selective evaluation of fungemia (n = 1), SFP (n = 9), pulmonary IFI (n = 1), convenient sampling (n = 1) and ICU patients (n = 2)
Mixed (infected non-infected)	5.0 (2.5-9.8)	20 studies, 98%	Low (17/20) and moderate (3/20)		Selective evaluation of fungemia (n = 3), pulmonary IFI (n = 7), convenient sampling (n = 4), ACLF patients (n = 10) and ICU patients (n = 9)
Risk of bias score				<0.01[†]	
4	11.6 (2.6-38.8)	4 studies, 94%	Moderate (4/4)		Selective evaluation of fungemia (n = 1), pulmonary IFI (n = 1), proven IFI (n = 1) convenient sampling (n = 4), infected sample (n = 1), ACLF patients (n = 2) and ICU patients (n = 1)
3	6.2 (4.1-9.2)	30 studies, 98%	Low (30/30)		Selective evaluation of fungemia (n = 2), SFP (n = 9), pulmonary IFI (n = 5), infected sample (n = 17), ACLF patients (n = 8) and ICU patients (n = 10)
1	0.8 (0.2-3.2)	4 studies, 95%	Low (4/4)		Selective evaluation of fungemia (n = 1), pulmonary IFI (n = 2) and convenient sampling (n = 1)

Note: FI: fungal infections, IFI: invasive fungal infections, CI: confidence interval, SFP: spontaneous fungal peritonitis, ICU: intensive care unit, ACLF: acute-on-chronic liver failure, SFP: spontaneous fungal peritonitis.

[§]random-effects model (DL method) for meta-analysis

[†]mixed-effects model for subgroup differences

[‡]random-effects model for subgroup differences

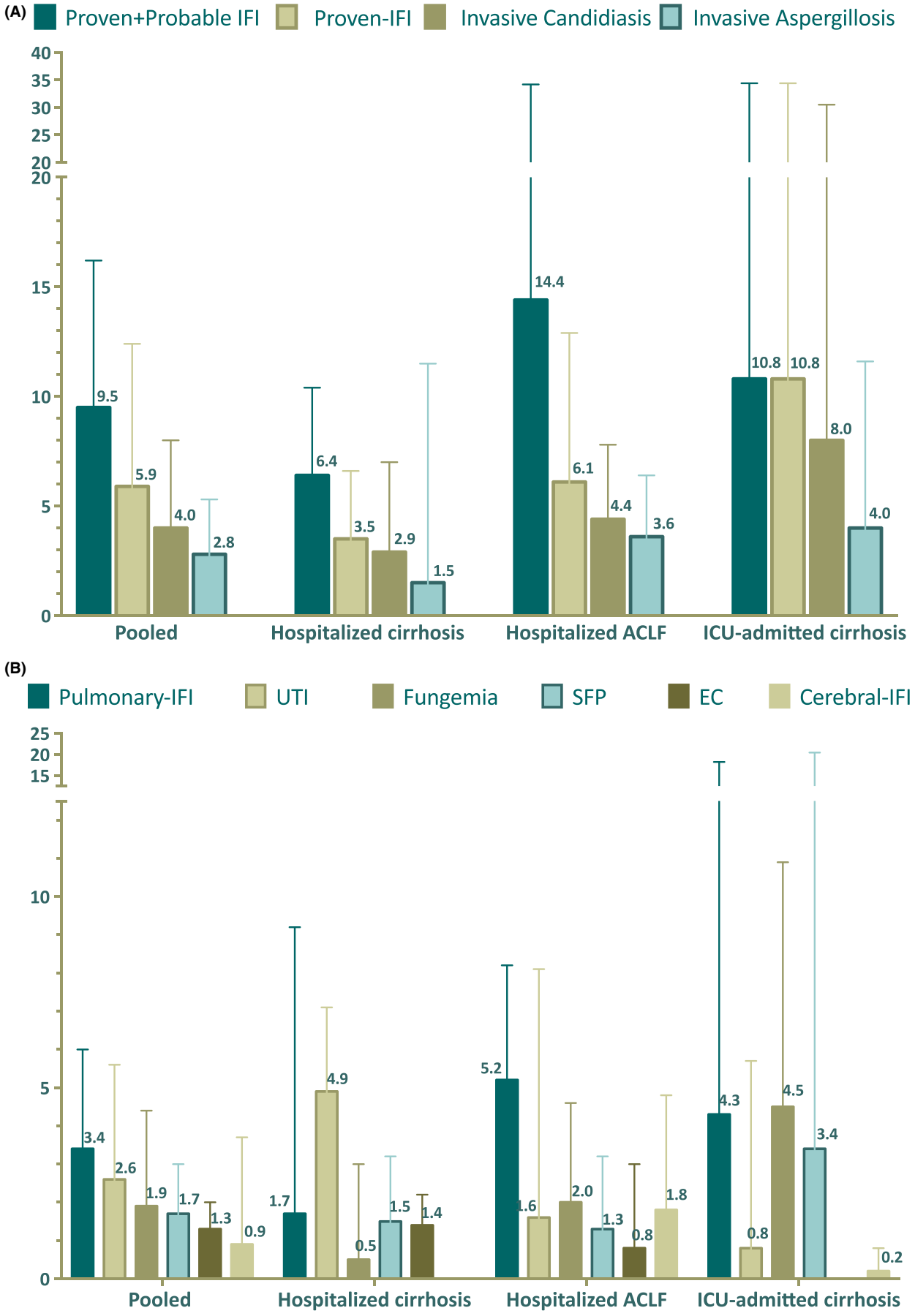

FIGURE 2 Legend on next page

FIGURE 2 Pooled estimates (percentage with 95% confidence intervals, CIs) of fungal infections (FIs) in cirrhosis
A. Type of FI, B. Site of FI, y-axis: percentage-pooled prevalence, x-axis: patient population, error bar: 95% CIs., ACLF: acute-on-chronic liver failure, ICU: intensive care unit, IFI: Invasive-FI, UTI: urinary tract infection, SFP: spontaneous fungal peritonitis and EC: Oesophageal candidiasis

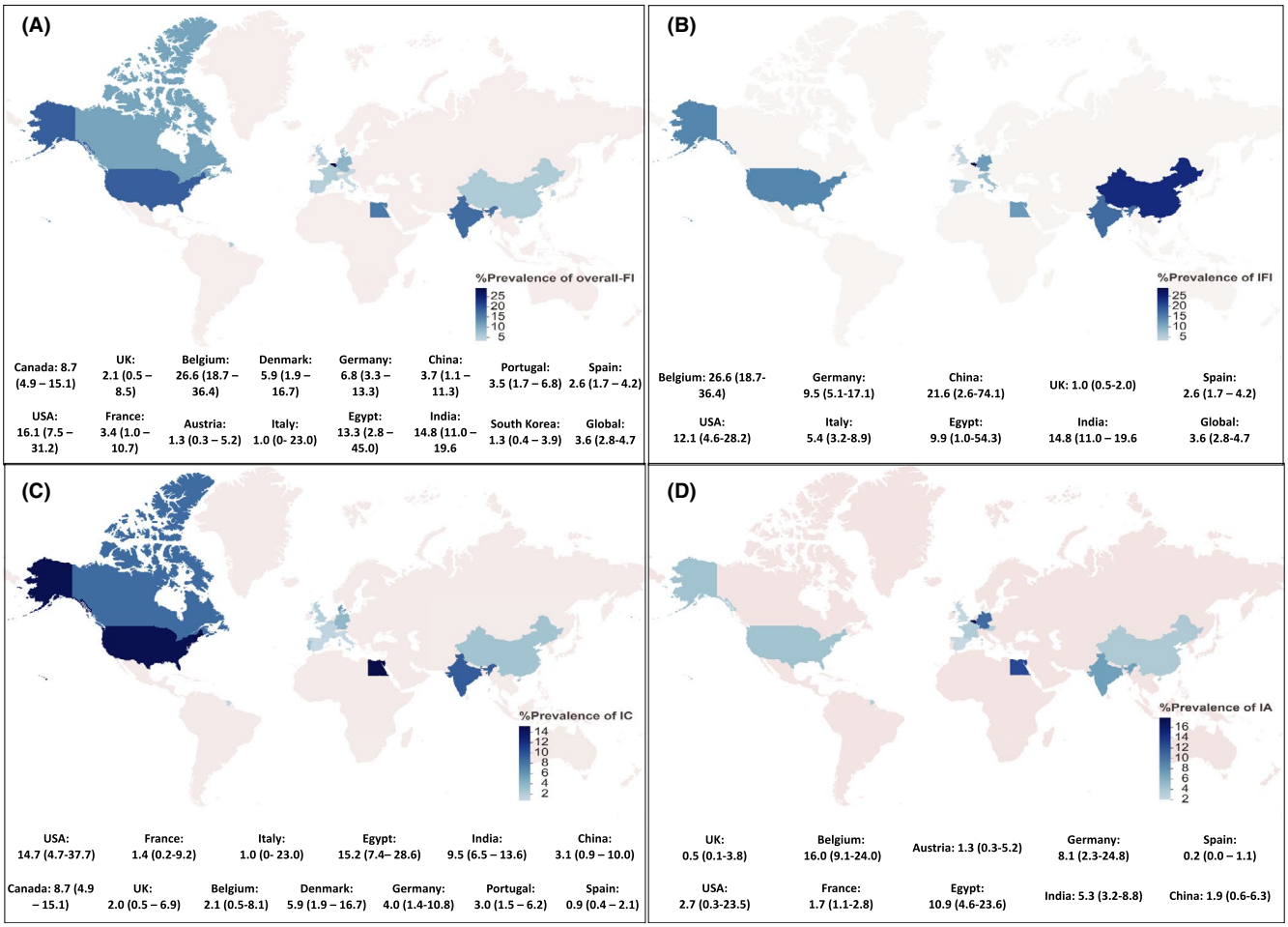

FIGURE 3 Geographical distribution of the pooled estimates (percentage with 95% confidence intervals) of fungal infections in cirrhosis
A. Overall fungal infections (overall FI), B. invasive fungal infections (IFIs), C. invasive candidiasis (IC) and D. invasive aspergillosis (IA)

variance in the estimates were sample size, population, year of conduct, country, age, Child-Pugh; CTP of the population, ICU admission, ROB score, MELD score of cases and prospective study design.

3.12 | Outlier testing and sensitivity analysis

Outlier studies (Figure S3) were identified for overall FI,[31,38,39,55] proven IFI,[55] IC,[39,55] IA,[38] pulmonary IFI,[25,38] fungal-UTI,[6,31,49,52] fungemia,[39] SFP[39] and leave-out plots demonstrated the influence of removing these studies on the prevalence estimates (FigureS 4-S12). Metaplots described the estimates of overall FI in cirrhosis according to the significant moderators (Figure S13). On excluding three studies[29,34,58] from the same database except one,[6] the pooled overall FI 10.0% (95% CI: 5.0%-19.0%) and IFI estimates 10.0% (95% CI: 5.0%-18.0%) were not much different from previously calculated estimates.

3.13 | Asymmetry in the estimates of FIs

The funnel plot and Egger's regression showed asymmetry in the estimates of overall FIs in cirrhosis ($P < .01$) (Figure S14). With sample size as a predictor, this plot's visual asymmetry was reduced. There was no asymmetry in the estimates of IFI ($P = .06$), IA ($P = .11$), SFP ($P = .06$), fungemia ($P = .21$) and UTI ($P = .29$) in cirrhosis. There was an asymmetry in the estimates of proven IFI ($P = .01$), IC ($P = .04$) and pulmonary IFI ($P = .02$) in cirrhosis. However, with 'sample size' as a predictor rather than 'standard error', the asymmetry in

the estimates of proven IFI ($P = .99$) and IC ($P = .08$) was abolished, though it persisted for pulmonary IFI estimates ($P < .01$).

4 | DISCUSSION

This review of studies from 4 continents and 15 countries has synthesised an estimate of overall FIs and IFIs as 10% (6%-17%) and 9.5% (5-16) in cirrhosis in-patients, respectively. This would equate to an annual projected burden of FIs in 1.6 million hospitalised patients with cirrhosis (considering the prevalence of in-patient cirrhosis as 10.6 million)[2] with an incurred yearly cost of $136 billion from a healthcare payer perspective (if cost per-FI is $84 790).[62] Pooled estimates of IC and IA in cirrhosis were 4% (2-8) and 3% (1.5-5.0), respectively, which would amount to 400,000 hospitalised cirrhosis patients with IC (associated cost: $61billion) and 320,000 hospitalised cirrhosis patients with IA (associated cost: $33 billion) annually.[2,62] These estimates significantly outnumber the global estimates of FIs in non-neutropenic ICU patients, which are 1.8% for IFIs, 1.6% for IC and 0.2% for IA.[63] A higher burden of FIs in cirrhosis is possibly due to endogenous reasons such as an altered mycobiome, neutrophil dysfunction, gastrointestinal barrier disruption or exogenous factors like frequent exposure to antibiotics, invasive procedures and repeated hospitalisations.[3,8] Pulmonary, urinary tract and bloodstream as the commonest infections favour exogenous factors as dominant predisposing factors for FIs in cirrhosis.

A trend of reduced prevalence was noted in most of the FIs over the last decade in cirrhosis. Consistently, a decline in IC incidence has also been reported between 2008 and 2013 in hospitalised patients from the United States[64] and is possibly related to improved infection-control policies with time. Intriguingly, IA's prevalence doubled in the past decade among cirrhosis. This finding was consistent with studies in other patient groups like chronic obstructive airway diseases[1] and is possibly linked to improvement in the diagnostics for aspergillosis. However, on a cautionary note, two out of four studies conducted more than a decade ago could have underreported IA's prevalence in cirrhosis. One study[28] reported only fungemia secondary to pulmonary aspergillosis, and another[31] did not report the aetiology of 15 cases of pulmonary IFI. These findings instigate a need for a surveillance network for FIs and their aetiologies over time in cirrhosis patients.

As a matter of concern, a rise in NAC species' incidence causing IC was noted over the past decade. Similar trends have also been observed recently among critically ill patients.[65] NACs represented 26%-36% of all *Candida* isolates from cirrhosis patients across North America, Europe and Asia. In recent years, *C glabrata* has been increasingly reported from Northern Europe and the United States, *C parapsilosis* from Spain and Brazil, and *C tropicalis* from Asia.[65] *C krusei and C glabrata* infections are particularly challenging due to relative resistance to azoles and high mortality.[66] Variations in antifungal susceptibility and poor outcomes associated with NAC species demand a need for their precise identification. We found 67.6% of NAC species were un-identified in cirrhosis, possibly due to the unavailability of modalities for species identification across centres, demanding robust diagnostics for FIs in general.

Geographic variations in the prevalence of FIs in cirrhosis were remarkably high, with the highest majority of overall FI from North America and Africa with further intra-continent variations like in Asia [India (15%)[56] and China (47%)[31]]. Endemic mycoses like coccidioidomycosis have been identified in cirrhosis patients from southwestern United States.[67] The pooled prevalence of IFIs among cirrhotics was highest in Asia (~20%). Tropical countries had a higher prevalence of IFIs, IC, pulmonary IFI, UTI, fungemia and SFP, possibly because such a climate is conducive for fungal growth.[1] The lower-middle-income countries had a higher prevalence of overall FIs, IFIs, IC, IA, pulmonary, urinary tract, bloodstream and peritoneal FIs suggesting an association of FIs with compromised health care, poor infection-control practices, misuse of antibiotics, lower socioeconomic status and environmental hygiene.[1]

Notably, the studies from ACLF and high disease severity patients had a higher prevalence of FIs, consistent with the literature.[61] The severity of liver failure and grade of ACLF have been linked to a greater degree of immune suppression and frequent hospitalisations that would explain such findings.[8] ICU-admitted cirrhotics had the highest burden of FIs, consistent with the existing literature.[68] Invasive devices, sedation, blood products use, low mobilisation, muscle weakness, multiple-broad-spectrum antibiotics, fungal colonisation and cross-infection are the common factors contributing to the FIs in ICU.[56] Therefore, cirrhosis patients, especially ACLF and ICU patients, represent a group with maximum predisposition and burden of FIs in cirrhosis. ACLF patients have been associated with higher mortality in IA[7], IC and EC patients.[69] Therefore, we recommend that ACLF and ICU admission may be included as host criteria for diagnosing IFIs in general.

Wide confidence intervals for the estimates of FIs in ICUs likely represent the variations in local practices, risk factors and regional epidemiology. Patients with infections in the denominator did not impact the prevalence of overall FIs and IFIs, possibly because one of the commonest reasons for hospitalisation in cirrhosis is infections.[3]

Strengths of this review include a comprehensive description of the global epidemiological trends of FIs in cirrhosis patients, rigorous methodology and thorough investigation of variation in estimates. Multiple types of FIs and cirrhosis of various severity and aetiologies were addressed. However, the inter-aetiology comparisons were not made due to insufficient data. The review would aid in deciding a baseline probability of FIs in cirrhosis patients. This is particularly important in cirrhosis, where the yield of fungal cultures is poor and invasive tissue sampling is often challenging, and biomarkers, for example Beta-D Glucan and Galactomannan, are critical for the diagnosis of FIs. Using this review, one can ascertain a pre-test probability of FIs, and later a post-test probability of FIs may be derived in a given patient using Fagan's nomogram and likelihood ratio of biomarkers.[71] Further, an appropriate antifungal may be initiated based on the regional epidemiology of FIs, for example Echinocandins for areas with a high prevalence of invasive candidiasis.

Asymmetry was evident in the estimates of FIs, which was reduced with sample size as a predictor and should be construed as clinical, methodological or sample size-related variance rather than 'publication bias'. The quality of evidence was satisfactory (90% studies at low ROB); however, most included studies had a ROB for possessing a special population or select evaluation of FIs for which multiple subgroup analyses were performed for meaningful estimates.

Under-reporting of FIs is possible in this review due to poor representation from lower-income countries, low yield of fungal diagnostics, lack of reporting of rare fungi and lack of local/national surveillance systems for FIs in cirrhosis. However, caution needs to be exercised. Even after excluding colonisation and possible IFIs, some of the included studies reported probable IFIs with *Candida* in the respiratory tract and urinary tract that may represent colonisation. Although fungal colonisation also carries a high mortality in cirrhosis,[33] temporal change in the prevalence of FIs and their species was based on a small number of studies and hence needs further validation.

5 | CONCLUSIONS

Despite variation in estimates and possible under-reporting, this review has demonstrated that FIs impose a significant disease burden in cirrhosis in-patients. FIs are predominantly nosocomial, and their estimates vary on temporal and geographical dimensions. ICU-admitted and ACLF patients have a high burden of IFIs and could be considered a host factor for defining IFIs. FIs are diverse and merit targeted evaluation and treatment in cirrhosis. A rise in NACs and aspergillus infections in cirrhosis are worrisome. Admission in public and private sector hospitals as a determinant of FIs and the economic burden of FIs should be explored. Epidemiology of FIs is crucial for selecting appropriate antifungals in cirrhosis patients.

5.1 | What You Need To Know?

Background

1. Fungal infections (FIs) are potentially lethal but often neglected in cirrhosis.
2. True epidemiology of FIs in cirrhosis is unknown.
3. We systematically reviewed the available literature on FIs in cirrhosis.

Findings

1. Pooled prevalence of overall FIs from 17 studies examining multiple FIs among cirrhosis was 10.2% (6.0-16.9).
2. *Candida* followed by *Aspergillus* was the commonest pathogen causing FIs in cirrhosis.
3. Lungs followed by urinary tract was the commonest site of FIs in cirrhosis.
4. Patients with FIs had a high disease severity scores and multi-organ failures.
5. Geographic variation was high in the estimates of FIs in cirrhosis.
6. Non-Albicans *Candida* and *Aspergillus* infections have increased over the last decade in cirrhosis.
7. ICU-admitted patients and those with ACLF had the highest estimates of FIs.

Implications

1. FIs should be extensively evaluated in cirrhosis in-patients to ensure early diagnosis and appropriate treatment of infections.
2. Regional epidemiology of FIs should be sought before diagnostic and therapeutic decisions for infections in cirrhosis.
3. Cirrhotics in ICU and ACLF represent a special group with highest burden of FIs and may be considered as host criteria for IFIs.

6 | TRIAL REGISTRATION NUMBER

N/A

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CONFLICT OF INTEREST

The authors do not have a commercial or other association that might pose a conflict of interest.

AUTHOR CONTRIBUTION

Nipun Verma: Conceptualization (lead); Data curation (lead); Formal analysis (lead); Methodology (lead); Project administration (equal); Software (lead); Supervision (lead); Validation (lead); Visualization (lead); Writing-original draft (lead); Writing-review & editing (lead). **Shreya Singh:** Data curation (equal); Methodology (equal); Writing-review & editing (equal). **Manvi Singh:** Data curation (equal); Writing-review & editing (equal). **Anil Chauhan:** Data curation (equal); Writing-review & editing (equal). **Pranita Pradhan:** Data curation (equal); Writing-review & editing (equal). **Nishant Jaiswal:** Formal analysis (supporting); Methodology (supporting); Writing-review & editing (supporting). **Arunaloke Chakrabarti :** Supervision (supporting); Writing-review & editing (equal). **Meenu Singh:** Conceptualization (equal); Data curation (equal); Funding acquisition (lead); Project administration (lead); Resources (equal); Writing-review & editing (equal).

ORCID

Nipun Verma https://orcid.org/0000-0003-4328-0914
Manvi Singh https://orcid.org/0000-0002-9653-1708

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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