Global prevalence of Infections and association of Regional Variations with Patient outcomes in Hospitalized Patients with Cirrhosis: a prospective cohort study for the CLEARED Consortium

Zhujun Cao, MD1, Florence Wong, MD2, Ashok K Choudhury, MD3, Patrick S Kamath, MD4, Mark Topazian, MD4, 5, Aldo Torre, MD6, Peter C Hayes, MD7, Jacob George, MD8, Ramazan Idilman, MD9, Wai-Kay Seto, MD10, Hailemichael Desalgn, MD5, Mario Reis Alvares-da-Silva, MD11, Brian Bush, MS12, Leroy R Thacker, PhD12, Qing Xie, MD1, Jasmohan S Bajaj, MD13 on behalf of the CLEARED Consortium

Affiliation:

1. Department of Infectious Diseases, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
2. Department of Medicine, University of Toronto, Toronto, ON, Canada
3. Department of Hepatology, Institute for Liver and Biliary Sciences, New Delhi, India
4. Division of Gastroenterology and Hepatology, Department of Internal Medicine, Mayo Clinic College of Medicine and Science, Rochester, MN, USA
5. Gastroenterology and Hepatology Unit, St Paul's Hospital, Millennium Medical College, Addis Ababa, Ethiopia
6. Department of Medicine, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico
7. Hepatology, Division of Health Sciences, Deanery of Clinical Sciences, University of Edinburgh, Edinburgh, UK
8. Storr Liver Centre, The Westmead Institute for Medical Research and Westmead Hospital, University of Sydney, Sydney, NSW, Australia

9. Department of Gastroenterology, Ankara University School of Medicine, Ankara, Turkey
10. Department of Medicine, School of Clinical Medicine, The University of Hong Kong, Hong Kong
11. Department of Hepatology, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil
12. Department of Population Health, Virginia Commonwealth University, Richmond, VA, USA
13. Division of Gastroenterology, Hepatology, and Nutrition, Department of Internal Medicine, Virginia Commonwealth University and Richmond Veterans Affairs Medical Center, Richmond, VA, USA

Drs Bajaj, Xie, Kamath, Topazian, Hayes, Seto, Torre, Idilman, George, Wong are full Professors.

Corresponding authors:

Jasmohan S Bajaj, MD

Professor of Medicine, Division of Gastroenterology, Hepatology, and Nutrition,

Virginia Commonwealth University and Richmond VA Medical Center,

1201 Broad Rock Boulevard

Richmond, VA 23249

Telephone: (804) 675 5802

Fax: (804) 675 5816

Email: jasmohan.bajaj@vcuhealth.org

Or

Qing Xie MD

Professor of Medicine, Department of Infectious Diseases

Shanghai Jiao Tong University School of Medicine

197 Ruijin Er Road

Shanghai 200025, China

Telephone: +86 13651804273

E-mail: xieqingrjh@163.com

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Table S6 and S7 has the full list of collaborators.

Abstract

Background: Infections have a poor prognosis in inpatients with cirrhosis, which vary worldwide. Aim**:** Determine variations in infections and their contribution in a contemporaneous cohort of cirrhosis inpatients **Methods**: For this prospective cohort study initiated by the CLEARED Consortium, patients were derived from a multinational database of hospitalized patients with cirrhosis admitted non-electively from countries across the income spectrum (high/middle/low). Infection details (site, organism, culture-positivity, drug-resistance (DR)) and association with outcomes (nosocomial infections, death) were compared between groups with/without infection. Multi-variable regression for hospitalization and 30-day death was performed. **Findings**: 4238 patients (98 centers, 26 countries, 56 years, 64% men) of whom 32% (n=1351) had admission infections were enrolled. Infected patients had worse severity of cirrhosis (MELD-Na 24 vs 19, p<0.0001), more infections (33.3% vs 13.3, p=<0.0001) and hospitalizations (53.2% vs 48.4%, p=0.003) within past 6 months and were higher in low/low-middle income countries (L/LMICs vs others, 41.7% vs 29.7%, p<0.0001). Most infections were spontaneous bacterial peritonitis (29%), respiratory (17%) and urinary infections (14%). Culture-positive infections were confirmed in only 42% of patients, lowest in Africa and China. Most of the isolated organisms were gram-negative (65%), then gram-positive (28%, highest in HICs) and fungi (7%). DR was seen in 22% of patients with culture-positive infections and highest in non-HICs. Outcomes: Patients with admission infections developed more nosocomial infections (17% vs 11%), ICU (25% vs 15%), in-hospital death (22% vs 8%), and 30-day death (30% vs 13%; all comparisons p<0.001). DROs were associated with greater mortality (in-hospital death: 33% vs 22%, P= 0.008, 30-day

death: 46% vs 29%, P< 0.0001). Infection increased odds of inpatient (aOR:2.3,1.86-2.83) and 30-day mortality (aOR:2.14,1.76-2.59) with non-HIC origin and cirrhosis severity parameters.

Interpretation: In the contemporaneous CLEARED consortium, presence of infection, causative organisms, and culture-positivity on admission vary substantially and associate with a high mortality risk in cirrhosis inpatients. Culture positivity, which guides appropriate antibiotics and prevents DR, is often hindered due to lack of appropriate resources.

Funding: None

RESEARCH IN CONTEXT

Evidence before this study

Infections are common in hospitalized patients with cirrhosis and negatively affect clinical outcomes. Available literature is largely region-specific. We searched PubMed for articles published from database inception to Nov 18, 2023, using the search terms “cirrhosis” AND ("bacterial infection" OR "fungal infection") AND ("global" OR "Worldwide") AND “prospective.” We found only one worldwide study (46 centers from 17 countries) of hospitalized patients with cirrhosis published in 2019 which enrolled only patients with infections. This study showed high prevalence of multi-drug resistant bacterial infection among studied centers but there were no low-income-countries (LICs) and only 5 middle-income countries (MICs) (India, Indonesia, Russia, Argentina, Brazil). Further, only infected patients were included leading to this not being representative of all admissions. The global burden of infection and drug-resistance organisms (DRO) needs to further investigation.

Added value of this study

In this study of the CLEARED Consortium from 98 centers, and 26 countries across six continents, 4238 non-electively hospitalized patients with cirrhosis were enrolled prospectively. We reported global and regional variations in the prevalence, characteristics and clinical outcomes of infections which were present in 32% of patients on admission. The highest proportion of admissions due to infection were in Low and LMICs who also had the highest proportion of gram-negative bacteria as causative organisms. Gram-positive causative organism representation was the highest in HICs.

Culture-positivity was seen in only 42% of patients with infections, which was lower in some sites possibly due to limited access to culture/ microbiology equipment. There was a higher burden of DRO infections in L/MICs.

On multi-variable logistic regression, patients not from HICs were at an approximate double odd of in-hospital death if they were admitted with an infection independently of known medical risk factors.

Implications of all the available evidence

There is a high burden of infections, and mortality in a worldwide consortium of hospitalized patients with cirrhosis. There are major regional variations in culture positivity, drug resistance, and causative organisms. There were poor outcomes related to infections in L/LMICs potentially due to the limited access to or inappropriate use of culture/ microbiology equipment or other aspects of infection care in these regions. This burden could be alleviated with provision of culture-related equipment and resources to optimize antibiotic use by encouraging routine culture in the case of suspected infections in these centers. A global perspective considering regional variations in infections, as well as resources available to diagnose, manage and treat infections in hospitalized patients with cirrhosis is needed to improve outcomes.

BACKGROUND:

Infections are a major cause of mortality worldwide with the highest burden in low- and low-middle-income countries (L/LMICs)[1-3]. Due to factors such as immunosuppression, frequent hospitalizations and antibiotic exposure, infections are common and have devastating consequences in cirrhosis[4 5-7] Additionally, regional variations in infection prevention and control and access to treatments, and prevalence of antimicrobial resistance (AMR)[8,9] can influence infection-related outcomes. Understanding the burden of infection at both global and regional levels is crucial to develop policies.

An international study of only infected inpatients with cirrhosis from mostly industrialized and few LMICs found regional variations[8]. Changing demographics, etiology, and antibiotic use since then requires an updated analysis in context of all admissions. The Chronic Liver Disease Evolution and Registry for Events and Decompensation (CLEARED) Consortium studies the worldwide determinants of mortality and previously found challenges across regions[10]. These challenges included limited laboratory and imaging infrastructure, microbiological capacity, and antimicrobial stewardship strategy, which together with the poor cirrhosis care, could lead to a significant burden of infection.

Our aims were to assess the associations of regional variations with infections in a global population of hospitalized patients with cirrhosis.

METHODS:

Study design

The CLEARED Consortium structure details have been published previously (supplement)[10]. Protocol and informed consent were approved by ethics committees of the participating centers.

Patients

Patients were screened consecutively from 98 centers in 26 countries across six continents (supplement, Figure S1/2, Table S1)[10]. After consent, adult patients who were non-electively hospitalized with confirmed cirrhosis were enrolled from November 2021-December 2022. A maximum of 50 patients/site was allowed.

Data management

Data were collected by site investigators and were overseen by steering committee members (supplement). The countries were also classified into high-income countries (HICs), upper middle-income countries (UMICs), LMICs, and LICs using World Bank definitions[11]. Data collected included demographics, comorbidities, cirrhosis details (complications within 6 months, MELD-Na), liver transplantation (LT) listing status, medication and reason(s) for admission, laboratory data, infections (admission/nosocomial/second), hospital course and organ dysfunction developed during the index admission and in-hospital outcome. Patients were followed-up for 30 days post-discharge using phone calls and record review to determine outcomes. De-identified aata were uploaded to a centralized data coordinating center.

Assessments and definitions

Published criteria (supplement) were used to define confirmed infections such as spontaneous bacteremia (SB), spontaneous bacterial peritonitis (SBP), lower respiratory tract infections (RTI), urinary tract infection (UTI), skin and soft tissue infection (SSTI),

bacterial entero-colitis, *Clostridioides difficile* diarrhea, procedure-related infections, spontaneous bacterial empyema, *etc*[12]. Clinically suspected but not confirmed infections were not counted as infections. All investigators were required to diagnose infection based on these definitions to ensure a homogenized inclusion and all patients were evaluated for infection daily till discharge.

Determination of admission vs nosocomial infections were according to the CDC's definitions for healthcare-associated infections. An infection is considered present on admission if the date of the first element used to meet the site-specific infection (supplement) is during the day of admission to an inpatient location and one calendar day after admission, *i.e.*, within 48 hours of admission, and those that occurred >48 hours post-admission were considered nosocomial. An infection separate from the original one at a different site or at a later date was a second infection. Each episode of infection was assessed to determine the type of infection, isolated organism(s), and resistance profile. Drug-resistant organisms (DRO) were defined as those resistant to specific antibiotics (supplement) which were not as stringent as traditional multi-drug resistance definitions. Other major clinical events during the index admission were also assessed and recorded including acute kidney injury (AKI) per International Club of Ascites (ICA)-AKI criteria[13], grade 3–4 hepatic encephalopathy (HE) per West Haven criteria, shock as defined by the use of vasopressors, use of mechanical ventilation, intensive care unit (ICU) transfer, hospice referral, LT receipt, and length of hospital stay.

Statistical analysis

The primary end point was in-hospital death or hospice referral in those with/without an admission infection. The secondary end points were death 30-day post-discharge,

nosocomial infections, organ dysfunction (AKI, grade 3–4 HE, mechanical ventilation, shock), need for ICU, as well as details of infections (culture positivity and distribution of infections, and DROs). Analysis of patients with versus those without infections on admission was performed for all outcomes. In addition, outcomes in only patients with infections on admission were studied. Characteristics of infections were compared across prespecified geographic regions. There was not *a priori* calculation of sample size for the primary end point of this study because we only allowed 50 patients per site. Multivariable logistic regression models were used to identify risk factors of inpatient and 30-day post-discharge death in all patients and in the sub-population of patients with admission infection by adjusting the prespecified covariates listed in the supplements.

Role of the funding source

No funding

RESULTS:

Patient characteristics

A total of 4238 patients worldwide fulfilling eligibility criteria were included during the study period. There were 1019 (24%) patients from mainland China, 686 (16.2%) from USA/Canada, 498 (11.8%) from India, 347 (8.2%) from Mexico, 304 (7.2%) from Europe, 296 (7.0%) from Australia, 276 (6.5%) from Africa, 281 (6.6%) from Turkey, 201 (4.7%) from South America, and 330 (7.8%) from the rest of Asia.

The mean age was 56.1±13.3 years and 64% were male; 1554 (36.7%) were from HICs, 1922 (45.2%) UMIC, and 762 (18.0%) for LMICs and LICs combined (Table 1). Etiologies were most often alcohol (1689, 39.9%) followed by viral hepatitis (1335, 31.5%) and metabolic dysfunction associated steatotic liver disease (726, 17.1%). A total of 1238 (29.3%) of patients had diabetes, 1047 (24.8%) had systemic hypertension and 582 (13.8%) had hyperlipidemia. More than half of the patients had previous history (within 6 months) of cirrhosis-related complications including 2702 (63.8%) with ascites, 1210 (28.6%) with variceal bleed, 1129 (26.7%) with overt HE, 707 (16.9%) with hyponatremia defined as a serum sodium of <130mmol/L, and 678 (16.1%) AKI. 2114 (50.0%) patients had been hospitalized and 832 (19.7%) had prior infections during the 6 months before admission and 401 (9.5%) were active on a LT waiting list.

3844 (90.7%) patients were admitted for liver-related reasons; among them the most common causes were anasarca (1439, 37.4%) closely followed by HE (1137, 29.6%), portal hypertensive gastrointestinal bleeding (960, 25.0%), AKI (879, 22.9%) and electrolyte abnormalities (872, 22.7%). At the time of patient admission, 1328 (31.3%) patients were already on β-blockers, 1787 (42.2%) on lactulose, 1019 (24.1%) rifaximin,

2259 (53.3%) on diuretics, 1818 (42.9%) on proton-pump inhibitors, 430 (10.2%) on statins, 560 (13.2%) on SBP prophylaxis and 757 (17.9%) on HBV antivirals.

Another 219 (5.9%) patients were admitted for reasons unrelated to liver or infection, mostly respiratory (27, 10.8% of other reasons), cardiac (26, 10.4%), or orthopedic (17, 6.8%) conditions.

Comparison between infected and uninfected groups:

A total of 1351 (32%) patients had evidence of a confirmed admission infection. Compared to patients without admission infection, those with infection had similar demographics, co-morbidities, etiology of cirrhosis apart from autoimmune/cholestatic conditions. A greater proportion of patients with infections were from LIC/LMICs and a relatively lower proportion from UMIC/HICs. As expected, patients admitted with an infection had higher previous cirrhosis-related complications, a higher number of recent hospitalizations and infections in the past 6 months and were more likely to be listed for LT (Table 1). Their more advanced liver disease severity was also reflected in medication use (diuretics, lactulose, rifaximin, and SBP prophylaxis) and laboratory values with higher WBC count, MELD-Na and Child scores among others (Table 1).

Infection characteristics and regional variations

Among those with admission infection, the most common was SBP followed by RTI, UTI, SB, SSTI and others (Figure 1A). By prespecified geographic regions, the prevalence of admission infection was highest in Mexican sites closely followed by Indian sites and African sites, while it was <40% in the remaining regions (Figure 1B). When site of infection was studied, SBP was highest in African, Turkish, and Chinese sites while RTI was more common in Chinese, European, and Australian sites. UTI was more common

in Mexican, USA/Canadian, Indian, and European sites; SB was higher in USA/Canadian, Indian, rest of Asian, and South American sites; and SSTI was more common in South American, USA/Canadian, Indian, and European sites (Figure 1C). Data regarding infection resolution was available in 960 patients, which took a median of 7 (IQR 5-10) days.

Organisms isolated and Prevalence of DROs:

Less than half of the patients (513/1234, 42%) had an organism isolated, and among these organisms, 332 (332/513, 65%) were gram-negative bacteria, 146 (146/513, 28%) were gram-positive bacteria and 35 (35/513, 7%) were fungi (Figure 1A). Centers from mainland China and Africa had highest rate of negative culture results followed by Turkey, South America, and Europe (Figure 1D). Culture positivity was relatively lower in African sites and mainland Chinese sites due to logistics related to culture collection and timely reporting, which was confirmed by direct inquiry from the sites.

In those who were culture positive, gram-negative bacteria were higher in Mexican, rest of Asian and Indian sites while gram-positive bacteria were higher in USA/Canadian, European, and Australian sites, and fungal infection was highest in Indian sites (Figure 1D). The overall distribution of causative organisms was gram-negative bacteria dominant across all geographic regions whereas the distribution of gram-positive bacteria was higher than one-third in several regions including USA/Canada (38/91, 41.7%), Europe (16/41, 39.0%), mainland China (18/42, 42.9%) and Turkey (6/18, 33.3%) (Figure 1E). In the subgroup that had a positive culture, DROs were found in 113 (113/513, 22%) patients (Figure 1A) with significant variations across regions (Figure 1F). DRO percentages,

relationship with rifaximin, and use of antibiotics in patients with admission infections by geographic region are in Table S2, S3 and S5.

Clinical outcomes

Demographics and clinical characteristics among patients who died/transferred to hospice versus those were summarized in Table S4.

In-hospital death or hospice referral occurred in 12.5% patients and was higher among those admitted with infection (299/1351, 22.1% vs. 232/2887, 8.0%, P< .0001). This negative association of admission infection extended to post-discharge period with higher deaths within 30 days of discharge (29.7% vs 12.6%, P< .0001).

Other negative outcomes, i.e., nosocomial infections, AKI, grade 3–4 HE, shock, ICU transfer, mechanical ventilation and hospital stay were higher in those admitted with infections (Table 2). Rates of inpatient LT were statistically similar.

In-hospital death or hospice referral rate was significantly higher in patients with DRO infections versus rest (37/113, 32.7% vs. 235/1084, 21.6%, P=0.008), which was also seen at 30-day post-discharge outcome (DROs 47/103, 45.6% vs. No-DRO, 284/989, 28.7%, P<0.0001).

Regression analysis for mortality

After adjusted all the prespecified covariates, the presence of infection on admission was associated with 2.3 times (95% CI 1.86-2.83) the odds of in-hospital mortality or hospice referral and 2.14 times (95% CI 1.76-2.59) the odds of death within 30 days of discharge (Figure 2AB). Patients with older age, female gender, not being in HICs, with AKI or HRS within 6 months, and higher MELD-Na score on admission also had increased risk of both in-hospital and 30-day post-discharge death (Figure 2AB). In-hospital death or hospice

referral was also associated with lactulose use on admission; no prior hospitalization in the past 6 months; and not being on diuretics, SBP prophylaxis, and HBV antivirals at the time of admission (Figure 2A). Patients on the LT list had reduced odds of death within 30 days of discharge (Figure 2B). Of 401 patients on the list, 61 (15.3%) underwent LT during the initial admission and 97 of 312 (31.1%) at 30-days post-discharge.

Among patients with infection, those with RTI (adjusted OR 1.79, 95% CI 1.14-2.81) had increased odds of in-hospital mortality or hospice referral compared with patients with other types of infection (Figure 2C). Older age, female gender, not being in HICs, previous HE and statin use and higher MELD-Na score on admission were also associated with in-hospital death and 30-day post-discharge death as well (Figure 2C/D). Previous AKI or HRS within 6 months of enrollment was associated with 30-day post-discharge death (Figure 2D). Within those with infections on admission, patients on diuretics and SBP prophylaxis at admission had reduced odds of in-hospital death or hospice referral (Figure 2C) and patients on the LT list had reduced odds of death within 30 days of discharge (Figure 2D).

DISCUSSION:

This global experience in more than 4000 hospitalized patients with cirrhosis shows the major importance of infections in determining the natural history during and 30-days after the hospitalization. The data demonstrate important variations across centers in the characteristics of infections, and resources available to manage these infections, which has an independent association with mortality.

Infections remain a scourge in patients with cirrhosis, with major implications on morbidity and mortality[4,5]. The altered gut barrier, gut microbiome, immune dysfunction, and repeated exposure to hospitalizations and antibiotics make infections particularly prevalent and challenging to manage in cirrhosis[4]. Early recognition, and appropriate therapy is needed to prevent progression of these infections to organ failures, death, and LT delisting. The current data provide important insights into the prevalence and consequences of infections across the world, especially in LMICs where such data are scarce. This is important as to patients from LMICs are exposed to increased risk factors of infection; decreased implementation of infection prevention and control facility; reduced diagnostic infrastructure and capacity, especially microbiology culture and antibiotic susceptibility test; limited access to the appropriate antibiotics ; and lack of antimicrobial stewardship measures to counter AMR[14]. The proportion of infections on admission involved almost a third of admitted patients, which is in line with prior regional consortia, but this was highest in L/LMICs. As expected, those with infections on admission were more likely to have a worse cirrhosis severity reflected by laboratory values, previous hospitalizations, and medication use. However, demographics, comorbid conditions (including statin use), and etiologies were statistically similar between groups This underlines the important role of cirrhosis severity and complications, rather than comorbid

conditions as predisposing factors for infections. Infections remain consequential with greater inpatient and 30-day mortality and other negative outcomes such as nosocomial infections, intensive care transfer as well as organ dysfunction. This was underscored by the higher mortality despite controlling for, etiology, medications, and not being in an HIC. While the higher rate of nosocomial infections, organ dysfunction and need for ICU care in infected patients is concerning since these are proximate outcomes towards mortality, there was a statistically similar rate of inpatient liver transplantation regardless of the presence of infections on admission. This could be due to the relatively low overall transplant rate and the lower likelihood of transplant delisting associated with the most common infections i.e., UTI and SBP[7]. Consistent with global sepsis data in general population, there was a significantly higher relative proportion of infections on admission in patients from L/LMICs, which was >40% in centers from Africa, India, and Mexico[2]. There could be several reasons for this disparity, such as lower resources for inpatient management, limited access to the appropriate antibiotics or higher antibiotic resistance, and lack of outpatient care targeted at prevention of infections, control of complications, and cirrhosis etiology control[4,10]. These specifically include control of ascites and hepatic encephalopathy, judicious SBP prophylaxis, and control/cure of viral hepatitis and other etiologies, which are likely to reduce the proportion of infections as cause of hospitalization in HICs[9]. Improving access to these interventions before/after the hospitalization in L/LMICs could potentially reduce the risk of infections and reduce these disparities.

We found significant differences in type and causative organisms of these infections across regions. As in prior studies, SBP was the most common infection followed by RTI,

UTI and SB[8,15]. Gram-negative infections followed by gram-positive and rare fungal causes were predominant causative organisms. A higher rate of gram-negative bacteria and fungi as causes were seen in L/LMICs, especially India, while HICs showed greater prevalence of gram-positive organisms[16]. While the exact reasons are unclear, adequate use of preventative medication such as SBP prophylaxis that predispose to gram-positive infections in HICs, and higher background use of antibiotics as inpatients and outpatients in L/LMICs could be contributory[17-19]. However, the overall interpretation of causative organisms is limited by only 42% infections being culture positive. This also meant a lower isolation of DROs, despite our relatively loose definition (22% of culture positive, i.e., or 9% of total infections), even in centers from India, unlike prior studies[8,20]. This is likely due to our focus on all admissions, and not just infections and limiting patients to 50 per site. While some organisms are fastidious, or cannot be routinely cultured (viruses, some fungi) using usual culture media, there are also other logistic obstacles[21]. These include recognition of potential infections, timely interventions such as paracentesis, and availability of equipment and laboratory services for performing and interpreting culture results. Some of these interventions are not performed in an effective and timely manner even in HICs[22]. A delayed sampling for cultures after empirical antibiotics could led to 50% decrease in sensitivity of pathogen detection in blood cultures[23]. Inadequate logistics in some sites in Africa and China was a major factor behind this low rate of positive cultures[24,25]. In areas with low detection rate of pathogens, the prevalence of infection was underestimated, those requiring causative organisms, e.g., SB, UTI, bacterial entero-colitis. The burden of DRO infection was also underestimated since isolation of organism is the basis for drug susceptibility test to classify DRO profile. These unique challenges

in management and diagnosis are consequential in determining outcomes, adequate antibiotic/antifungal treatment(s), spread of DRO and need to be acknowledged when interpreting infection results. More efforts are needed to enhance resources to prevent the spread of AMR worldwide.

We found that women were at higher risk of death in-hospital for all patients, and within infected patients. Gender-related disparities are complex with lower LT listing, higher susceptibility to alcohol, higher prevalence of immunosuppressives for autoimmune disease, and lower healthcare access to women compared to men contributing[26,27]. While the diuretics and SBP prophylaxis were linked with a lower mortality on multivariable opposite to the univariable findings; there is a risk of multi-collinearity. When studying only infected patients, higher age, MELD score, female sex, and not being in a HIC were associated with mortality. However, statin use, HE, and RTI were uniquely related to higher mortality in those with admission infections. The role of HE and statins were also seen in the 30-day mortality model.

Statin use, while potentially beneficial in compensated cirrhosis, are not that helpful do not have similar effects in decompensated patients, but the mechanism(s) are unclear[28]. Statin use could also be a marker of cardiovascular dysfunction and interact with antibiotics. HE is not captured adequately by the MELD-Na, therefore this may add another layer of mortality risk and aspiration associated with HE could result in RTI[29]. RTI is related to pneumonia, in addition to aspiration due to HE and GI bleeding[29,30]. This can lead to respiratory failure and has a poor prognosis, explaining the association with mortality.

Our findings update and extend global and regional consortia that focus on inpatient cirrhosis outcomes into a contemporaneous worldwide cohort with equitable representation across centers. Piano et al published important findings that showed high rates of antibiotic resistance in selected sites from a global consortium of infected inpatients with cirrhosis [8]. Notably, in that study, Africa, China, and Australia were not represented. Due to barriers related to culture positivity, including uninfected and infected patients, and the 50-patient maximum per site, our rates of DROs were lower, even among Indian sites. We found that worse cirrhosis severity, and higher age were associated with inpatient and 30-day mortality[8]. Higher gram-positive in HICs, including Europe, USA, Canada, and Australia, extended Europe-wide studies and provides context related to causative organisms in other parts of the world.

Our study is limited by the nature of study design, as with any observational study that the associations seen may not be causal. Despite our efforts to control for known variables, the possibility of residual confounding remains. The study was also limited by the relatively small number of patients per site which could lead to selection bias, lack of uniform antibiotic protocols across sites, and lack of granularity regarding patterns of culture sampling, history of antibiotics before sampling and individual organisms isolated. Finally, some sites were going through the COVID-19 pandemic, even though we excluded these patients. Despite these shortcomings, we have the most equitable representation of centers worldwide that provides a unique insight into the global disparities of morbidity and mortality of infection in inpatients with cirrhosis.

In this global consortium of prospectively enrolled inpatients with cirrhosis, infections are associated with a high risk of inpatient and 30-day mortality despite controlling for

cirrhosis severity, co-morbid conditions, and location of the patients. Patients in L/LMICs are more prone to being admitted with infections, which in turn have a worse prognosis in those individuals. There are substantial variations in types of infection, culture-positivity rate, which are determined partly by availability of equipment for culture and interpretation. A global perspective which considers variations in infections and resources available to diagnose, manage and treat infections in hospitalized patients with cirrhosis is needed to improve outcomes.

Contributors:

JSB was the co-principal investigator of the consortium, was on the steering committee, and contributed to conceptualization, investigation, data collection, data analysis, data interpretation, writing the original draft of the manuscript, and reviewing and editing the manuscript. ZC was on the steering committee and contributed to study design, data collection, data analysis and visualization, data interpretation, writing the original draft of the manuscript, and reviewing and editing the manuscript. QX and FW was on the steering committee and contributed to data curation, validation, investigation, study design, data collection, data interpretation, and reviewing and editing the manuscript. AKC was the co-principal investigator of the consortium, was on the steering committee, and contributed to data collection, data analysis, data interpretation, investigation, and reviewing and editing the manuscript. PSK, MT, AT, PCH, JG, RI, WKS, HD and MRA-d-S were on the steering committee and contributed to study design, data collection, data analysis, data interpretation, investigation, and reviewing and editing the manuscript. BJB contributed to data curation, project administration, methodology, supervision, and reviewing and editing the manuscript. LRT contributed to data analysis, data curation, project administration, data interpretation, methodology, supervision, validation and visualization, and reviewing and editing the manuscript. The remaining authors in the CLEARED Investigators group led the local recruitment efforts at their site, entered data, and provided feedback on all data and manuscripts generated. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. JSB, BJB, and LRT accessed and verified the data underlying the study.

Declaration of interests: none for any author

Data sharing: The individual data collected will not be made available due to restrictions from ethics boards.

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Figure legends:

Figure 1: Overall view of infection characteristics.

DRO: drug-resistant organism, SBP: spontaneous bacterial peritonitis, RTI: respiratory tract infection, UTI: urinary tract infection, SB: spontaneous bacteremia, SSTI: skin and soft tissue infection.
Comparisons performed using Chi-square tests.

Figure 1A: Types of infection, culture positivity, distribution of causative organisms and rate of DRO.
Figure 1B: Prevalence of infection on admission among all enrolled patients by different regions.
Figure 1C: Types of infection by different regions.
Figure 1D: Isolation of causative organisms by regions.
Figure 1E: Distribution of organisms among isolated bacteria and fungi by regions.
Figure 1F: Prevalence of DRO infection among patients with positive culture results by regions.

Figure 2: Forest plots for logistic regression for inpatient and 30-day post-discharge mortality in all patients and patients with infection on admission
OR: odds ratio, L/LMIC: low and low-middle income countries, UMIC: Upper-middle income countries, HIC: high-income countries, AKI: acute kidney injury, HRS: hepatorenal syndrome, SBP: spontaneous bacterial peritonitis, MELD-Na: model for end-stage liver disease sodium, RTI: respiratory tract infection, UTI: urinary tract infection, SB: spontaneous bacteremia, SSTI: skin and soft tissue infection.
Details on all variables considered in the univariable analysis are provided in the appendix (p 4-5); those that met the significance level as described in the Methods and were significant on multivariable analysis are presented here.
Figure 2A: Odds ratios and 95% CI for in-hospital death or hospice transfer in all patients
Figure 2B: Odds ratios and 95% CI for 30-day post-discharge mortality in all patients

Figure 2C: Odds ratios and 95% CI for in-hospital death or hospice transfer in patients with infection on admission

Figure 2D: Odds ratios and 95% CI for 30-day post-discharge mortality in patients with infection on admission

References:

1. Allegranzi B, Bagheri Nejad S, Combescure C, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. Lancet 2011; 377(9761): 228-41.
2. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet 2020; 395(10219): 200-11.
3. Collaborators GBDAR. Global mortality associated with 33 bacterial pathogens in 2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2022; 400(10369): 2221-48.
4. Bajaj JS, Kamath PS, Reddy KR. The Evolving Challenge of Infections in Cirrhosis. N Engl J Med 2021; 384(24): 2317-30.
5. Arvaniti V, D'Amico G, Fede G, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterology 2010; 139(4): 1246-56, 56 e1-5.
6. Allen AM, Kim WR, Moriarty JP, Shah ND, Larson JJ, Kamath PS. Time trends in the health care burden and mortality of acute on chronic liver failure in the United States. Hepatology 2016; 64(6): 2165-72.
7. Reddy KR, O'Leary JG, Kamath PS, et al. High risk of delisting or death in liver transplant candidates following infections: Results from the North American Consortium for the Study of End-Stage Liver Disease. Liver Transpl 2015; 21(7): 881-8.
8. 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.
9. Fernandez J, Piano S, Bartoletti M, Wey EQ. Management of bacterial and fungal infections in cirrhosis: The MDRO challenge. J Hepatol 2021; 75 Suppl 1: S101-S17.
10. Bajaj JS, Choudhury AK, Xie Q, et al. Global disparities in mortality and liver transplantation in hospitalised patients with cirrhosis: a prospective cohort study for the CLEARED Consortium. Lancet Gastroenterol Hepatol 2023; 8(7): 611-22.

11. https://datatopics.worldbank.org/world-development-indicators/the-world-by-income-and-region.html.
12. Bajaj JS, O'Leary JG, Reddy KR, et al. Second infections independently increase mortality in hospitalized patients with cirrhosis: the North American consortium for the study of end-stage liver disease (NACSELD) experience. Hepatology 2012; 56(6): 2328-35.
13. Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. Gut 2015; 64(4): 531-7.
14. Abdula N, Macharia J, Motsoaledi A, Swaminathan S, VijayRaghavan K. National action for global gains in antimicrobial resistance. Lancet 2016; 387(10014): e3-5.
15. Bajaj JS, O'Leary JG, Tandon P, et al. Nosocomial Infections Are Frequent and Negatively Impact Outcomes in Hospitalized Patients With Cirrhosis. Am J Gastroenterol 2019; 114(7): 1091-100.
16. 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.
17. Wong F, Piano S, Singh V, et al. Clinical features and evolution of bacterial infection-related acute-on-chronic liver failure. J Hepatol 2021; 74(2): 330-9.
18. Fernandez J, Prado V, Trebicka J, et al. Multidrug-resistant bacterial infections in patients with decompensated cirrhosis and with acute-on-chronic liver failure in Europe. J Hepatol 2019; 70(3): 398-411.
19. Bajaj JS, Rodriguez MP, Fagan A, et al. Impact of bacterial infections and spontaneous bacterial peritonitis prophylaxis on phage-bacterial dynamics in cirrhosis. Hepatology 2022; 76(6): 1723-34.
20. Verma N, Divakar Reddy PV, Vig S, et al. Burden, risk factors, and outcomes of multidrug-resistant bacterial colonisation at multiple sites in patients with cirrhosis. JHEP Rep 2023; 5(8): 100788.
21. Li B, Hong C, Fan Z, et al. Prognostic and therapeutic significance of microbial cell-free DNA in plasma of people with acute decompensation of cirrhosis. J Hepatol 2023; 78(2): 322-32.

22. Patel N, Silvey S, O'Leary JG, et al. Early paracentesis is associated with better prognosis compared with late or no-paracentesis in hospitalized veterans with cirrhosis and ascites. Liver Transpl 2023; 29(9): 919-27.
23. Cheng MP, Stenstrom R, Paquette K, et al. Blood Culture Results Before and After Antimicrobial Administration in Patients With Severe Manifestations of Sepsis: A Diagnostic Study. Ann Intern Med 2019; 171(8): 547-54.
24. Fleming KA, Horton S, Wilson ML, et al. The Lancet Commission on diagnostics: transforming access to diagnostics. Lancet 2021; 398(10315): 1997-2050.
25. Jacobs J, Hardy L, Semret M, et al. Diagnostic Bacteriology in District Hospitals in Sub-Saharan Africa: At the Forefront of the Containment of Antimicrobial Resistance. Front Med (Lausanne) 2019; 6: 205.
26. Samra R, Hankivsky O. Adopting an intersectionality framework to address power and equity in medicine. Lancet 2021; 397(10277): 857-9.
27. O'Leary JG, Wong F, Reddy KR, et al. Gender-Specific Differences in Baseline, Peak, and Delta Serum Creatinine: The NACSELD Experience. Dig Dis Sci 2017; 62(3): 768-76.
28. Pose E, Napoleone L, Amin A, et al. Safety of two different doses of simvastatin plus rifaximin in decompensated cirrhosis (LIVERHOPE-SAFETY): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Gastroenterol Hepatol 2020; 5(1): 31-41.
29. Bajaj JS, O'Leary JG, Tandon P, et al. Targets to improve quality of care for patients with hepatic encephalopathy: data from a multi-centre cohort. Aliment Pharmacol Ther 2019.
30. Xu L, Ying S, Hu J, et al. Pneumonia in patients with cirrhosis: risk factors associated with mortality and predictive value of prognostic models. Respir Res 2018; 19(1): 242.

Appendix

Steering Committee:

USA	Jasmohan Bajaj, Richmond, USA
India	Ashok Choudhury, Delhi, India
Canada, and Continental Europe	Florence Wong, Toronto, Canada
Mainland China	Qing Xie, Shanghai, China
Mexico	Aldo Torre, Mexico City, Mexico
Hong Kong and rest of Asia	Wai Kay Seto, Hong Kong
South America	Mario Reis, Porto Alegre, Brazil
Turkey	Ramazan Idilman, Ankara, Turkey
Australia	Jacob George, Sydney, Australia
Africa and Middle East	Mark Topazian, Addis Ababa, Ethiopia
	Hailemichael Desalegn, Addis Ababa, Ethiopia
	Patrick Kamath, Mayo Clinic, Rochester, USA
United Kingdom	Peter Hayes, Edinburgh, UK

Eligibility criteria

Inclusion criteria:

1. Cirrhosis
2. Admitted for non-elective reasons
3. Age >18 years
4. Able to consent or have a legal representative who can consent

Exclusion criteria:

1. Acute liver failure
2. Unable to consent
3. Admitted electively
4. Life expectancy <48 hours
5. Prisoners
6. HCC without loco-regional control for >6 months or patients on systemic therapy for HCC currently
7. COVID-19 diagnosis confirmed during the current admission
8. Known recent MI (<6 months) or stroke with residual defects

Definitions of Infections:

1. **Spontaneous bacteremia:** *positive blood cultures* in the absence of any recognized source of infection
2. **Spontaneous Bacterial Peritonitis**: Ascitic fluid polymorphonuclear cells *>250/ml* with or without positive fluid bacterial cultures;
3. **Spontaneous bacterial empyema:** Pleural fluid polymorphonuclear cells *>250/ml* with or without positive fluid bacterial cultures or gram stain;
4. **Pneumonia**
    A. Radiographically confirmed pneumonia on CXR or CT scan AND
    B. Presence of:
        i. At least 1 respiratory symptom (cough, sputum production, dyspnea, tachypnea, pleuritic pain) with
        ii. At least 1 finding on auscultation (rales or crepitation) or 1 sign of infection (core body temperature >38ºC, shivering or leucocyte count >10,000/mm3or <4,000/mm3) in the absence of antibiotics.
5. **Bacterial entero-colitis:** diarrhea or dysentery with a positive stool culture for Salmonella / Shigella / Yersinia/ Campylobacter/ pathogenic E. coli.
6. **Urinary tract infection:** Urine WBC count >15 cells per high-power field, symptoms and positive urine culture
7. **Clostridium difficile diarrhea:** diarrhea with a positive C. difficile assay
8. **Skin infection:** Fever and cellulitis associated with leukocytosis
9. **Procedure related infections**
10. **Other infections** (e.g. cholangitis, diverticulitis) will be diagnosed according to clinical, radiological, and bacteriologic data

Classification of drug-resistant organism: fluoroquinolone resistance organism, carbapenemase producing Enterobacteriaceae, methicillin resistant staphylococcus aureus, vancomycin resistant enterococcus and other unspecified resistant organisms.

Statistical analysis:

Descriptive statistics were summarized with means and SDs or medians and IQRs for continuous variables appropriately, and percentages and frequencies for categorical variables. The normality of continuous variable was assessed by examination of QQ plots. Assessment of homogeneity of variance for the two-sample *t*-test were made using the Folded F-test while the assessment of homogeneity of variance for one-way ANOVA was done using Bartlett's test. Comparisons of continuous variables between two groups were done with a two-sample *'t'* test for normally distributed data and Mann–Whitney U test for non-normally distributed data. Comparisons of continuous variables among three or more groups were done with one-way ANOVA for normally distributed data and Kruskal–Wallis test for non-normally distributed data. When homogeneity of variance was rejected, p-values for the *t*-test are from the unequal variance two-sample t-test (Satterthwaite) and for the one-way ANOVA from Welch's test. Comparisons of categorical data were done with the χ^2 test when no expected cell count was less than 1 and at most 20% of expected cell counts less than 5, otherwise Fisher's exact test was utilized. Multivariable logistic regression models were used to estimate the effect of infection on outcomes by adjusting the prespecified covariates. The assumption of linearity in the logit for all continuous variables was assessed by first creating categorical variables from the continuous variables using cuts at 10%, 25%, 50%, 75%, and 90% and then fitting two models with these categorized continuous variables, one treating the variable as a factor (categorical) and a second treating the variables as continuous. A likelihood ratio test was then performed comparing the full model (factors) to the reduced model (continuous) and if there was no significant difference, the simpler model was utilized. In all cases we found no need to utilize the more complicate model. Models were built using a modified "purposeful selection of covariates" as described by Hosmer, Lemeshow, and Sturdivant[1]. Variables that were different between the infection groups at the $\alpha=0.25$ were considered for model entry. A backward

elimination procedure was then used, with a significance level of α=0.05 required to stay in the model. After this parsimonious model was arrived at, all previously removed variables were added back one at a time and retained only if they achieved the α=0.05 significance level in the final model. This multivariable approach was used to predict inpatient death or hospice referral and 30-day post-discharge death in all patients and in the sub-population of patients with admission infection. All analyses were done using SAS 9.4 or R 4.3.1 (http://www.r-project.org/), and, unless otherwise specified, with an α=0.05 significance level for all tests.

The following variables were considered in the multi-variable analysis:

Inpatient death or hospice referral in all patients: Age, Male Sex, Diabetes, Hypertension, Hyperlipidemia, Prior Variceal Bleed, Prior HE, Prior Ascites, Prior Hydrothorax, Prior AKI or Hepatorenal Syndrome, Prior Hyponatremia, Prior Transplant Listing, Hospitalized in the Past 6mos, Infections in the Prior 6mos, Admission Betablockers, Admission Lactulose, Admission Rifaximin, Admission Diuretics, Admission Statins, Admission SBP Prophylaxis, Admission Antivirals, World-Bank Income Group, Liver Related Admission, Infections at Admission or within the first 48 Hours, Admission MELD-Na

Inpatient death or hospice referral in patients with admission infection: Age, Male Sex, Diabetes, Hypertension, Hyperlipidemia, Prior Variceal Bleed, Prior HE, Prior Ascites, Prior Hydrothorax, Prior AKI or Hepatorenal Syndrome, Prior Hyponatremia, Prior Transplant Listing, Hospitalized in the Past 6mos, Infections in the Prior 6mos, Admission Betablockers, Admission Lactulose, Admission Rifaximin, Admission Diuretics, Admission Statins, Admission SBP Prophylaxis, Admission Antivirals, World-Bank Income Group, Admission MELD-Na, Type of infection

30-day post-discharge mortality in all patients: Age, Male Sex, Diabetes, Hypertension, Hyperlipidemia, Prior Variceal Bleed, Prior HE, Prior Ascites, Prior Hydrothorax, Prior AKI or Hepatorenal Syndrome, Prior Hyponatremia, Prior Transplant Listing, Hospitalized in the Past 6mos, Infections in the Prior 6mos, Admission Betablockers, Admission Lactulose, Admission Rifaximin, Admission Diuretics, Admission Statins, Admission SBP Prophylaxis, Admission

Antivirals, World-Bank Income Group, Liver Related Admission, Infections at Admission or within the first 48 Hours, Admission MELD-Na

30-day post-discharge Mortality in patients with admission infection: Age, Male Sex, Diabetes, Hypertension, Hyperlipidemia, Prior Variceal Bleed, Prior HE, Prior Ascites, Prior Hydrothorax, Prior AKI or Hepatorenal Syndrome, Prior Hyponatremia, Prior Transplant Listing, Hospitalized in the Past 6mos, Infections in the Prior 6mos, Admission Betablockers, Admission Lactulose, Admission Rifaximin, Admission Diuretics, Admission Statins, Admission SBP Prophylaxis, Admission Antivirals, World-Bank Income Group, Admission MELD-Na, Type of infection

Figure S1: Flowchart of patients enrolled.

Figure S2: Map of countries that have centers where patients were enrolled for CLEARED

Supplementary Table 1 Geographic distribution of participating centers

Region Classification	Number of Patients, n (%)	Number of Sites, n (%)
US/Canada	686 (16.2%)	15 (15.3%)
Mexico	347 (8.2%)	7 (7.1%)
Mainland China	1019 (24.0%)	23 (23.5%)
India	498 (11.8%)	11 (11.3%)
Australia	296 (7.0%)	8 (8.2%)
Africa	276 (6.5%)	8 (8.2%)
South America	201 (4.7%)	6 (6.1%)
Turkey	281 (6.6%)	6 (6.1%)
Rest of Asia	330 (7.8%)	7 (7.1%)
Europe	304 (7.2%)	7 (7.1%)
TOTAL	4,238 (100.0%)	98 (100.0%)

Supplementary Table 2 Prevalence of drug-resistant organism in all patients with admission infection by geographic region

	USA/Canada (*n* = 165)	**Mexico (*n* = 143)**	**Mainland China (*n* = 253)**	**India (*n* = 181)**	**Australia (*n* = 74)**	**Africa (*n* = 93)**	**South America (*n* = 48)**	**Turkey (*n* = 43)**	**Rest of Asia (*n* = 107)**	**Europe (*n* = 90)**
Drug-resistant organisms, n (%)	25 (15.2)	24 (16.8)	15 (5.9)	13 (7.2)	4 (5.4)	7 (7.5)	7 (14.6)	4 (9.3)	11 (10.3)	3 (3.3)
	USA/Canada (*n* = 25)	**Mexico (*n* = 24)**	**Mainland China (*n* = 15)**	**India (*n* = 13)**	**Australia (*n* = 4)**	**Africa (*n* = 7)**	**South America (*n* = 7)**	**Turkey (*n* = 4)**	**Rest of Asia (*n* = 11)**	**Europe (*n* = 3)**
Fluoroquinolone resistance organism, n (%)	4 (16.0)	8 (33.3)	4 (26.7)	4 (30.8)	1 (25.0)	2 (28.6)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)
Vancomycin resistant enterococcus, n (%)	6 (24.0)	1 (4.2)	0 (0.0)	0 (0.0)	2 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Methicillin resistant staphylococcus aureus, n (%)	5 (20.0)	0 (0.0)	5 (33.3)	1 (7.7)	0 (0.0)	0 (0.0)	1 (14.3)	1 (25.0)	0 (0.0)	0 (0.0)
Other, n (%)	10 (40.0)	15 (62.5)	6 (40.0)	8 (61.5)	1 (25.0)	5 (71.4)	5 (71.4)	3 (75.0)	11 (100)	3 (100)

Supplementary Table 3 Antibiotic use in all patients with admission infections by geographic regions

	USA/Canada (*n* = 172)	**Mexico (*n* = 143)**	**Mainland China (*n* = 257)**	**India (*n* = 194)**	**Australia (*n* = 79)**	**Africa (*n* = 109)**	**South America (*n* = 53)**	**Turkey (*n* = 49)**	**Rest of Asia (*n* = 120)**	**Europe (*n* = 95)**
Any antibiotics use, n (%)	167 (97.1)	140 (97.9)	225 (99.2)	193 (99.5)	76 (96.2)	109 (100.0)	52 (98.1)	49 (100.0)	113 (94.2)	93 (97.9)
	USA/Canada (*n* = 167)	**Mexico (*n* = 140)**	**Mainland China (*n* = 225)**	**India (*n* = 193)**	**Australia (*n* = 76)**	**Africa (*n* = 109)**	**South America (*n* = 52)**	**Turkey (*n* = 49)**	**Rest of Asia (*n* = 113)**	**Europe (*n* = 93)**
Beta lactams, n (%)	97 (58.1)	97 (69.3)	130 (51.0)	88 (45.6)	49 (64.5)	65 (59.6)	31 (59.6)	42 (85.7)	57 (50.4)	54 (58.1)
Fluoroquinolones, n (%)	15 (9.0)	4 (2.9)	55 (21.6)	37 (19.2)	9 (11.8)	27 (24.8)	7 (13.5)	5 (10.2)	4 (3.5)	12 (12.9)
Zosyn/Timentin/Augmentin, n (%)	45 (27.0)	1 (0.7)	70 (27.5)	32 (16.6)	6 (7.9)	2 (1.8)	8 (15.4)	0 (0.0)	32 (28.3)	15 (16.1)
Clindamycin, n (%)	4 (2.4)	3 (2.1)	1 (0.4)	8 (4.2)	1 (1.3)	0 (0.0))	2 (3.9)	1 (2.0)	6 (5.3)	2 (2.2)
Vancomycin, n (%)	58 (34.7)	18 (12.9)	10 (3.9)	28 (14.5)	4 (5.3)	8 (7.3)	6 (11.5)	5 (10.2)	11 (9.7)	5 (5.4)
Daptomycin, n (%)	7 (4.2)	3 (2.1)	1 (0.4)	2 (1.0)	0 (0.0)	0 (0.0)	1 (1.9)	1 (2.0)	3 (2.7)	4 (4.3)
Macrolides, n (%)	5 (3.0)	5 (3.6)	1 (0.4)	2 (1.0)	3 (4.0)	6 (5.5)	2 (3.9)	0 (0.0)	5 (4.4)	2 (2.2)
Tetracyclines, n (%)	7 (4.2)	2 (1.4)	3 (1.2)	18 (9.3)	3 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	5 (5.4)
Anti-fungal, n (%)	11 (6.6)	8 (5.7)	20 (7.8)	54 (28.0)	2 (2.6)	3 (2.8)	0 (0.0)	1 (2.0)	7 (6.2)	3 (3.2)
Imipenem/Meropenem/Ertapenem, n (%)	15 (9.0)	56 (40.0)	60 (23.5)	109 (56.5)	7 (9.2)	15 (13.8)	9 (17.3)	11 (22.5)	27 (23.9)	16 (17.2)
Metronidazole, n (%)	9 (5.4)	10 (7.1)	2 (0.8)	6 (3.1)	3 (4.0)	24 (22.0)	2 (3.9)	3 (6.1)	9 (8.0)	4 (4.3)
Linezolid, n (%)	3 (1.8)	7 (5.0)	11 (4.3)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Other, n (%)	36 (21.6)	9 (6.4)	28 (11.0)	50 (25.9)	26 (34.2)	24 (22.0)	3 (5.8)	2 (4.1)	18 (15.9)	15 (16.1)

Supplementary Table 4 Demographics and clinical characteristics between patients with and without in-hospital mortality/discharge to hospice

Characteristic	In-Hospital Mortality / Discharge to Hospice		P value
	No (n = 3707)	Yes (n = 531)	
Age, y, mean ± SD	56.2 ± 13.28	55.9 ± 13.16	0.707
Male sex, n (%)	2372 (64.0)	339 (63.8)	0.948
World Bank Income Group, n (%)			<0.0001
Low Income or Lower Middle Income	594 (16.0)	168 (31.6)	
Upper Middle Income	1707 (46.1)	215 (40.5)	
High Income	1406 (37.9)	148 (27.9)	
Etiology of cirrhosis, n (%)			
Alcohol use	1449 (39.1)	240 (45.2)	0.007
Nonalcoholic fatty liver disease	631 (17.0)	95 (17.9)	0.62
Hepatitis B	823 (22.2)	63 (11.9)	<0.0001
Hepatitis C	396 (10.7)	53 (10.0)	0.62
Auto-immune hepatitis or cholestasis	380 (10.3)	68 (12.8)	0.073
Cryptogenic	279 (7.5)	46 (8.7)	0.36
Other[a]			
Comorbidities, n (%)			
Diabetes	1101 (29.8)	137 (26.0)	0.001
Hypertension	914 (24.8)	133 (25.3)	0.79
Hyperlipidemia	514 (13.9)	68 (12.9)	0.53
Cirrhosis related history, n (%)			
Ascites	2330 (62.9)	372 (70.2)	<0.0001
Variceal bleed	1058 (28.6)	152 (28.7)	0.97
Overt hepatic encephalopathy	927 (25.0)	202 (38.1)	<0.0001
Hyponatremia	568 (15.5)	139 (26.5)	<0.0001
Acute kidney injury or hepatorenal syndrome	564 (15.3)	146 (27.6)	<0.0001
Hydrothorax	314 (8.5)	41 (7.7)	0.56
Hospitalized in past 6 months	1847 (49.9)	267 (50.4)	0.83
Infections in past 6 months	682 (18.4)	150 (28.3)	<0.0001
Listed for liver transplant	339 (9.2)	62 (11.7)	0.062
Medications on admission, n (%)			
β-blockers	1171 (31.6)	157 (29.6)	0.35
Diuretics	1992 (53.8)	267 (50.3)	0.13
Lactulose	1476 (39.8)	311 (58.6)	<0.0001
Rifaximin	836 (22.6)	183 (34.5)	<0.0001
SBP prophylaxis	474 (12.8)	86 (16.2)	0.029
Statins	385 (10.4)	45 (8.5)	0.18
Proton-pump inhibitors	1588 (42.9)	230 (43.5)	0.78
HBV antivirals	705 (19.1)	52 (9.8)	<0.0001
Liver-related admission[b], n (%)	3344 (90.2)	500 (94.2)	0.003
Anasarca, n/N (%)	1252/3344 (37.4)	187/500 (37.4)	0.98

Hepatic encephalopathy, n/N (%)	867/3344 (25.9)	270/500 (54.0)	<0.0001
Gastrointestinal bleeding, n/N (%)	847/3344 (25.3)	208/500 (12.6)	0.19
Acute kidney injury, n/N (%)	598/3344 (17.9)	281/500 (56.2)	<0.0001
Electrolyte abnormalities, n/N (%)	663/3344 (19.8)	209/500 (41.8)	<0.0001
Hepatitis B flare, n/N (%)	240/3344 (7.2)	8/500 (1.6)	0.004
Liver and infection unrelated admission[c]	363 (9.8)	31 (5.8)	0.003
Lab data at admission[d], median (IQR)	/		/
hemoglobin, g/dL	11.0 (8.8, 14.6)	9.8 (8.0, 12.1)	<0.0001
white cell count, 10^6 cells/mL	6.4 (4.2, 10.3)	10.0 (6.5, 17.4)	<0.0001
international normalized ratio	1.5 (1.3, 1.8)	1.9 (1.5, 2.5)	<0.0001
sodium, mmol/L	136.0 (131.9,139.0)	131.4 (127.8,136.0)	<0.0001
creatinine, mg/dL	1.1 (0.7, 3.0)	1.6 (1.0, 3.0)	<0.0001
aspartate transaminase, U/L	56.0 (35.0, 105.0)	83.0 (47.0, 136.0)	<0.0001
alanine aminotransferase, U/L	33.0 (21.0, 57.0)	42.0 (24.0, 65.1)	<0.0001
total bilirubin, mg/dL	4.5 (1.6, 18.0)	8.7 (3.3, 22.0)	<0.0001
albumin, g/dL	3.2 (2.7, 3.7)	2.7 (2.2, 3.3)	<0.0001
Disease severity at admission, median (IQR)			
Child Pugh score*	9 (7, 11)	11 (10, 13)	<0.0001
MELD-Na score*	20 (14, 26)	29 (24, 33)	<0.0001

NOTE. Percentages may not total 100 because of rounding. SD denotes standard deviation, IQR interquartile range, SBP spontaneous bacterial peritonitis, HBV hepatitis B virus. Where denominators differed from the overall group totals, values are presented as n/N (%).

To convert values for bilirubin from mg/dL to μmol/L, multiply by 17.1. To convert values for creatinine from mg/dL to μmol/L, multiply by 88.4.

[a]Common etiology included 53 drug induced liver injury, 37 schistosomiasis, 21 Wilson's disease, 17 hemochromatosis.

[b]Percentages exceed 100% because of multiple cause of admission in an individual patient.

[c]Common reason included 27 respiratory, 26 cardiac and 17 orthopedic.

[d]There are 224 missing observations for Child Pugh score and 233 for MELD-Na score.

Supplementary Table 5 Information on drug-resistant organism in patients with admission infection and on Rifaximin

	USA/Canada (*n* = 61)	**Mexico (*n* = 57)**	**Mainland China (*n* = 21)**	**India (*n* = 110)**	**Australia (*n* = 24)**	**Africa (*n* = 22)**	**South America (*n* = 8)**	**Turkey (*n* = 18)**	**Rest of Asia (*n* = 18)**	**Europe (*n* = 16)**
Drug-resistant organisms, n (%)	8 (13.1)	14 (24.6)	1 (4.8)	6 (5.5)	1 (4.2)	1 (4.5)	4 (50.0)	3 (16.7)	2 (11.1)	1 (6.3)
	USA/Canada (*n* = 8)	**Mexico (*n* = 14)**	**Mainland China (*n* = 1)**	**India (*n* = 6)**	**Australia (*n* = 1)**	**Africa (*n* = 1)**	**South America (*n* = 4)**	**Turkey (*n* = 3)**	**Rest of Asia (*n* = 2)**	**Europe (*n* = 1)**
Fluoroquinolone resistance organism, n (%)	1 (12.5)	5 (35.7)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vancomycin resistant enterococcus, n (%)	3 (37.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Methicillin resistant staphylococcus aureus, n (%)	1 (12.5)	0 (0.0)	1 (100.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)
Other, n (%)	3 (37.5)	9 (64.3)	0 (0.0)	4 (66.7)	0 (0.0)	1 (100.0)	3 (75.0)	2 (66.7)	2 (100)	1 (100)

Supplementary Table 6 Center and region-wise breakdown of subjects enrolled

Site Name	Region Classification	Two-Character Country Code	Number Enrolled
Akdeniz University	Turkey	TR	50
All India Institute of Medical Sciences	India	IN	50
Apollo Hospitals	India	IN	17
Asian Institute of Gastroenterology	India	IN	50
Baylor University Medical Center Dallas	US/Canada	US	50
Beijing Youan Hospital, Capital Medical University	China	CN	50
CHU de Cocody	Africa	CI	50
CMC Vellore	India	IN	50
Hospital De Especialidades “Dr. Antonio Fraga Mouret” Centro Médico Nacional La Raza, Imss.	Mexico	MX	50
Centro Mexico	Mexico	MX	50
Changi General Hospital Singapore	Rest of Asia	SG	41
Cleveland Clinic Abu Dhabi	Rest of Asia	AE	49
Columbia University Medical Center	US/Canada	US	21
Duke University	US/Canada	US	25
Ege University	Turkey	TR	50
Gaziantep University	Turkey	TR	43
Glasgow Royal Infirmary	Europe	GB	47
Health Sciences Centre, Manitoba	US/Canada	CA	44
Hippokration General Hospital, Athens	Europe	GR	31
Hospital Britannico de Buenos Aires	South America	AR	4
Hospital Civil de Guadalajara Fray Antonio Alcalde	Mexico	MX	50
Hospital Federal de Bonsucesso	South America	BR	37
Hospital General de México "Dr. Eduardo Liceaga"	Mexico	MX	47
Hospital General Dr. Manuel Gea Gonzalez	Mexico	MX	50
Hospital Italiano Buenos Aires	South America	AR	50
Hospital das Sciencas da Faculdade de Medicina da Universidade de Sao Paulo	South America	BR	50
Hospital de Clinicas de Porto Alegre	South America	BR	23
ILBS Hospital Delhi	India	IN	33
Ibn Sina Specialized Hospital	Africa	SD	33
Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Mexico City	Mexico	MX	50
Instituto de Salud Digestiva	Mexico	MX	50
Jaslok Hospital	India	IN	50
John Hunter Hospital	Australia	AU	50
Jos University	Africa	NG	31
KIMS Bhubaneswar	India	IN	49

Site Name	Region Classification	Two-Character Country Code	Number Enrolled
King Chulalongkorn Memorial Hospital	Rest of Asia	TH	49
Liverpool Hospital	Australia	AU	2
Maputo Central Hospital	Africa	MZ	3
Marmara University	Turkey	TR	50
Mayo Clinic - Jacksonville	US/Canada	US	50
Mayo Clinic - Scottsdale	US/Canada	US	50
Mayo Clinic - Rochester	US/Canada	US	49
Mengchao Hepatobiliary Hospital of Fujian Medical University	China	CN	50
Mercy Medical Center	US/Canada	US	49
Mersin University	Turkey	TR	40
Minia University	Africa	EG	48
Mustapha University Hospital	Africa	DZ	50
Nanfang Hospital, Southern Medical University	China	CN	44
Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School	China	CN	26
NIHR Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and University of Nottingham, Nottingham	Europe	GB	50
PGIMER Chandigarh	India	IN	50
Pontificia Universidad Catholica de Chile	South America	CL	37
Prince of Wales Hospital	Australia	AU	50
Queen Elizabeth Hospital Birmingham	Europe	GB	50
Rela Institute	India	IN	50
Ren Ji Hospital, Shanghai Jiao Tong University	China	CN	44
Richmond VAMC	US/Canada	US	48
Royal Berkshire Hospital	Europe	GB	50
Royal Infirmary of Edinburgh	Europe	GB	28
Royal North Shore Hospital	Australia	AU	23
Royal Perth Hospital	Australia	AU	50
Ruijin Hospital	China	CN	47
Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow	India	IN	50
Second Affiliated Hospital of Chongqing Medical University	China	CN	49
Second Hospital of Shandong University	China	CN	38
Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine	China	CN	49
Singapore General	Rest of Asia	SG	50
Sir Charles Gairdner Hospital	Australia	AU	22
Sir Ganga Ram Hospital	India	IN	49

Site Name	Region Classification	Two-Character Country Code	Number Enrolled
St George Liver Clinic	Australia	AU	50
St. Paul's Hospital Millennium Medical College	Africa	ET	49
Tel Aviv Sourasky Medical Center	Rest of Asia	IL	41
University of Hong Kong	Rest of Asia	HKSAR/CN	50
The Fifth People's Hospital of Suzhou	China	CN	50
The First Affiliated Hospital of Guangxi Medical University	China	CN	48
The First Affiliated Hospital of Nanchang University	China	CN	42
The First Affiliated Hospital of Wenzhou Medical University	China	CN	49
The First Hospital of Jilin University	China	CN	50
The First People's Hospital of LanZhou	China	CN	9
The Second XiangYa Hospital of Central South University	China	CN	50
The Third Affiliated Hospital of Hebei Medical University	China	CN	50
The Third Affiliated Hospital of Sun Yat-sen University	China	CN	36
The Third People's Hospital of Guilin	China	CN	45
University of Toronto	US/Canada	CA	50
Traditional Chinese Medicine Hospital of Xinjiang Uygur Autonomous Region	China	CN	50
Ankara University	Turkey	TR	48
UMC Freiburg	Europe	DE	48
Union Hospital, Tongji Medical College, Huazhong University of Science and Technology	China	CN	49
University of Alberta	US/Canada	CA	50
University of Malaya Medical Centre	Rest of Asia	MY	50
University of Pennsylvania	US/Canada	US	50
University of Pittsburgh	US/Canada	US	50
University of Washington	US/Canada	US	50
Virginia Commonwealth University	US/Canada	US	50
WDGMC, Johannesburg	Africa	ZA	12
West China Hospital of Sichuan University	China	CN	48
Westmead Hospital	Australia	AU	49
Zhongshan Hospital, Fudan University	China	CN	46

Supplementary Table 7 C.L.E.A.R.E.D. Collaborators, Affiliations, and Email addresses

Site ID	Site Name	Author Name	Author email address
AE-01	Cleveland Clinic Abu Dhabi	Shiva Kumar	kumars5@clevelandclinicabudhabi.ae
AR-02	Hospital Italiano de Buenos Aires, Argentina	Adrián Gadano	adrian.gadano@hospitalitaliano.org.ar
AR-02	Hospital Italiano de Buenos Aires, Argentina	Sebastián Marciano	sebastian.marciano@hospitalitaliano.org.ar
AU-01	Westmead Hospital, Sydney	Fiona Tudehope	fiona.tudehope2@svha.org.au
AU-03	John Hunter Hospital, Newcastle	Alexander Prudence	Alexander.Prudence@health.nsw.gov.au
AU-03	John Hunter Hospital, Newcastle	Robert Gibson	robert.gibson@health.nsw.gov.au
AU-04	St George Liver Clinic	Amany Zekry	a.zekry@unsw.edu.au
AU-05	Royal Perth Hospital, Perth	Adam Doyle	Adam.Doyle@health.wa.gov.au
AU-05	Royal Perth Hospital, Perth	Hooi Ling Si	hooi.si@health.wa.gov.au
AU-06	Royal North Shore Hospital	Yu Sung Kim	Yusung.kim@health.nsw.gov.au
AU-06	Royal North Shore Hospital	Cameron Gofton	Cameron.Gofton@health.nsw.gov.au
AU-07	Prince of Wales Hospital, Sydney	Stephen Riordan	Stephen.Riordan@health.nsw.gov.au
AU-08	Sir Charles Gairdner Hospital	Gerry MacQuillan	Gerry.MacQuillan@health.wa.gov.au
BR-01	Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil	Matheus Michalczuk	matheusm01@hotmail.com
BR-02	Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo	Alberto Farias	albertoqfarias@gmail.com
BR-02	Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo	Patricia Zitelli	patricia.momoyo@hc.fm.usp.br
BR-03	Hospital Federal de Bonsucesso	Gustavo Pereira	ghspereira@gmail.com
BR-03	Hospital Federal de Bonsucesso	Livia Victor	lbvictor@gmail.com
CA-01	University of Toronto	Chinmay Bera	chinmay.bera@uhn.ca
CA-02	University of Manitoba, Winnipeg	Nabiha Faisal	Nabiha.Faisal@umanitoba.ca
CA-26	University of Alberta, Edmonton	Monica Dahiya	mdahiya@ualberta.ca
CA-26	University of Alberta, Edmonton	Puneeta Tandon	ptandon@ualberta.ca
CI-01	CHU de Cocody, Abidjan, Cote dIvoire	Marie Jeanne Lohoues	lohoueskouacoumj@gmail.com
CI-01	CHU de Cocody, Abidjan, Cote dIvoire	Ponan Claude Regis Lah	clauderegis146@gmail.com
CL-01	Pontificia Catholic University of Chile, Santiago	Carlos Benítez	benitezc@gmail.com
CL-01	Pontificia Catholic University of Chile, Santiago	Marco Arrese	marrese@uc.cl
CN-03	The Third People's Hospital of Guilin	Jing Guan	11845839@qq.com
CN-03	The Third People's Hospital of Guilin	Yongchao Xian	xianyongchao0901@163.com
CN-04	The Fifth People's Hospital of Suzhou	Chuanwu Zhu	zhuchw@126.com
CN-04	The Fifth People's Hospital of Suzhou	Yingling Wang	306823363@163.com

CN-05	The First Affiliated Hospital of Guangxi Medical University	Man Su	493541173@qq.com
CN-05	The First Affiliated Hospital of Guangxi Medical University	Minghua Su	smh9292@163.com
CN-06	The First Hospital of Jilin University	Xinrui Wang	xinrui_9@126.com
CN-06	The First Hospital of Jilin University	Yanhang Gao	15804303019@163.com
CN-07	The Second XiangYa Hospital of Central South University	Feng Peng	pf6034@csu.edu.cn
CN-07	The Second XiangYa Hospital of Central South University	Yongfang Jiang	jiangyongfang@csu.edu.cn
CN-08	The Third Affiliated Hospital of Hebei Medical University	Caiyan Zhao	zhaocy2005@163.com
CN-08	The Third Affiliated Hospital of Hebei Medical University	Wei Wang	wangwei_1211@126.com
CN-09	Second Hospital of Shandong University	Dedong Yin	2574797886@qq.com
CN-09	Second Hospital of Shandong University	Lei Wang	wlcrb@sdu.edu.cn
CN-11	The First Affiliated Hospital of Wenzhou Medical University	Mingqin Lu	lmq0906@163.com
CN-11	The First Affiliated Hospital of Wenzhou Medical University	Yijing Cai	caiyijing007@163.com
CN-12	Traditional Chinese Medicine Hospital of Xinjiang Uygur Autonomous Region	Feng Guo	gf_sj@163.com
CN-12	Traditional Chinese Medicine Hospital of Xinjiang Uygur Autonomous Region	Xiaozhong Wang	wxz125@sina.com
CN-13	Zhongshan Hospital, Fudan University	Ningping Zhang	zhang.ningping@zs-hospital.sh.cn
CN-13	Zhongshan Hospital, Fudan University	Wanqin Zhang	zhang.wanqin1@zs-hospital.sh.cn
CN-14	School of Medicine, Ren Ji Hospital, Shanghai Jiao Tong University	Fuchen Dong	dongfuchen66@163.com
CN-14	School of Medicine, Ren Ji Hospital, Shanghai Jiao Tong University	Hai Li	haili_17@126.com
CN-15	Department of Infectious Disease, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China	Jing Liu	jingliu_21@hust.edu.cn
CN-15	Department of Infectious Disease, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China	Xin Zheng	xinz@hust.edu.cn
CN-16	Center of Infectious Disease, West China Hospital of Sichuan University	Hong Tang	htang6198@hotmail.com
CN-16	Center of Infectious Disease, West China Hospital of Sichuan University	Libo Yan	yanlibo725@aliyun.com
CN-17	Beijing Youan Hospital, Capital	Bin Xu	xubin1016@126.com

	Medical University		
CN-17	Beijing Youan Hospital, Capital Medical University	Linlin Wei	llmm0830@126.com
CN-18	The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou	Zhen Xu	chilamxu@hotmail.com
CN-18	The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou	Zhiliang Gao	gaozhl@mail.sysu.edu.cn
CN-19	Mengchao Hepatobiliary Hospital of Fujian Medical University	Haibing Gao	gaohb605@163.com
CN-19	Mengchao Hepatobiliary Hospital of Fujian Medical University	Minghua Lin	lmh543@163.com
CN-20	The First Affiliated Hospital of Nanchang University	Qunfang Rao	raoqunfang@163.com
CN-20	The First Affiliated Hospital of Nanchang University	Xiaoping Wu	wuxiaoping2823@aliyun.com
CN-21	Nanfang Hospital, Southern Medical University	Beiling Li	lbling123@163.com
CN-21	Nanfang Hospital, Southern Medical University	Jinjun Chen	chjj@smu.edu.cn
CN-22	Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine	Chenghai Liu	chenghailiu@hotmail.com
CN-22	Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine	Yanyun Zhang	m15159804011@163.com
CN-23	Second Affiliated Hospital of Chongqing Medical University	Huan Deng	denghuan_537@126.com
CN-23	Second Affiliated Hospital of Chongqing Medical University	Peng Hu	hp_cq@163.com
CN-24	Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School	Jian Wang	13063335263@163.com
CN-24	Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School	Jie Li	lijier@sina.com
DE-01	UMC Freiburg (University Medical Center Freiburg)	Dominik Bettinger	dominik.bettinger@uniklinik-freiburg.de
DE-01	UMC Freiburg (University Medical Center Freiburg)	Michael Schultheiß	michael.schultheiss@uniklinik-freiburg.de
DZ-01	Mustapha Bacha University Hospital, Algiers	Hibat Allah Belimi	hib-2009@live.fr
DZ-01	Mustapha Bacha University Hospital, Algiers	Nabil Debzi	nabildebzi@yahoo.fr
EG-01	Minia University, Egypt	Alaa Mostafa	alaam.mostafa2022@gmail.com
EG-01	Minia University, Egypt	Yasser Fouad	yasser.abdallah@mu.edu.eg
ET-01	St Paul's Hospital Millenium Medical College, Addis Ababa, Ethiopia	Henok Fisseha	henok_fisseha@yahoo.com
GB-01	NIHR Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and University of Nottingham, Nottingham	Suresh Vasan Venkatachalapathy	suresh.venkatachalapathy@nhu.nhs.uk
GB-01	NIHR Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust	Aloysious D Aravinthan	aloysious.aravinthan@nottingham.ac.uk

	and University of Nottingham, Nottingham. Nottingham Digestive Diseases Centre, Translational Medical Sciences, School of Medicine, University of Nottingham, Nottingham.		
GB-02	Queen Elizabeth University Hospitals, Birmingham	Neil Rajoriya	neil.Rajoriya@uhb.nhs.uk
GB-02	Queen Elizabeth University Hospitals, Birmingham	Rosemary Faulkes	rosemary.Faulkes@uhb.nhs.uk
GB-04	Glasgow Royal Infirmary	Damien Leith	damien.Leith@ggc.scot.nhs.uk
GB-04	Glasgow Royal Infirmary	Ewan Forrest	ewan.Forrest@ggc.scot.nhs.uk
GB-05	Royal Berkshire Hospital	Adebayo Danielle	danielle.Adebayo@royalberkshire.nhs.uk
GB-05	Royal Berkshire Hospital	James Kennedy	james.Kennedy@royalberkshire.nhs.uk
GB-06	Royal Infirmary of Edinburgh	Diana Yung	diana.yung@nhslothian.scot.nhs.uk
GR-01	2nd Department of Medicine, Medical School, Natinal & Kapodistrian University of Athens, Hippokration General Hospital, Athens, Greece	Alexandra Alexopoulou	alexopou@ath.forthnet.gr
GR-01	2nd Department of Medicine, Medical School, Natinal & Kapodistrian University of Athens, Hippokration General Hospital, Athens, Greece	Iliana Mani	ilianamani@windowslive.com
HK-01	School of Clinical Medicine, The University of Hong Kong	James Fung	jfung@gastro.hk
IL-01	Tel-Aviv Sourasky Medical Center, Tel Aviv, Israel	Helena Katchman	helenak@tlvmc.gov.il
IL-01	Tel-Aviv Sourasky Medical Center, Tel Aviv, Israel	Liane Rabinowich	lianer@tlvmc.gov.il
IN-02	Jaslok Hospital, Mumbai	Ajay Jhaveri	ajayjhaveri@gmail.com
IN-02	Jaslok Hospital, Mumbai and Apollo Hospital, Navi Mumbai	Aabha Nagral	aabhanagral@gmail.com
IN-03	Asian institute of Gastroenterology, Hyderabad	Anand Kulkarni	anandvk90@gmail.com
IN-03	Asian institute of Gastroenterology, Hyderabad	Mithun Sharma	drmithunsharma@gmail.com
IN-04	Institute of Liver and Biliary Sciences, Delhi	Shiv K Sarin	shivsarin@gmail.com
IN-05	Christian Medical College, Vellore	Ashish Goel	drashishgoel@cmcvellore.ac.in
IN-05	Christian Medical College, Vellore	C E Eapen	eapen@cmcvellore.ac.in
IN-06	PGIMER, Chandigarh	Ajay Duseja	ajayduseja@yahoo.co.in
IN-06	PGIMER, Chandigarh	Akash Gandotra	akkigandotra4@gmail.com
IN-07	AIIMS, New Delhi	Anoop Saraya	ansaraya@yahoo.com
IN-07	AIIMS, New Delhi	Jatin yegurla	drjatin.y@gmail.com
IN-08	Dr. Rela Institute and Medical Centre, Chennai	Dinesh Jothimani	dinesh.jothimani@relainstitute.com
IN-08	Dr. Rela Institute and Medical Centre, Chennai	Mohammad Rela	mohamedrela@gmail.com
IN-09	Sir Ganga Ram Hospital, Delhi	Anil Arora	anilarora@sgrh.com
IN-09	Sir Ganga Ram Hospital, Delhi	Ashish Kumar	ashishk10@yahoo.com

IN-10	Sanjay Gandhi Postgraduate Institute of Medical Research, Lucknow	Akash Roy	royakash12@gmail.com
IN-10	Sanjay Gandhi Postgraduate Institute of Medical Research, Lucknow	R K Dhiman	rkpsdhiman@gmail.com
IN-11	KIMS, Bhubaneswar, Odisha	A C Anand	ac.anand@kims.ac.in
IN-11	KIMS, Bhubaneswar, Odisha	Dibyalochan Praharaj	dibyalochan.praharaj@kims.ac.in
MX-01	Centro Médico ISSEMYM	Araceli Bravo Cabrera	chelybrca@gmail.com
MX-01	Centro Médico ISSEMYM	Sarai Gonzalez Hueso	saraigh69@yahoo.com
MX-02	Hospital General de México "Dr. Eduardo Liceaga"	José Luis Pérez Hérnandez	josluiperez@hotmail.com
MX-02	Hospital General de México "Dr. Eduardo Liceaga"	Oscar Morales Gutierrez	droscarmorales@hotmail.com
MX-03	Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Mexico City	Abraham Ramos-Pineda	dr.abrahamramos@gmail.com
MX-03	Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Mexico City	Godolfino Miranda Zazueta	godomiranda25@gmail.com
MX-04	Centro Médico la Raza, Mexico City	Mauricio Castillo Barradas	mcbarradas@hotmail.com
MX-05	Instituto de la Salud Digestiva, Guadalajara	Lilian Torres Made	liliantorresmade@yahoo.com
MX-05	Instituto de la Salud Digestiva, Guadalajara	Rene Male Velazquez	renemale@gmail.com
MX-06	Hospital Civil de Guadalajara Fray Antonio Alcalde, Guadalajara	Francisco Félix-Tellez	ftellezmd@gmail.com
MX-06	Hospital Civil de Guadalajara Fray Antonio Alcalde, Guadalajara	José Antonio Velarde-Ruiz Velasco	velardemd@yahoo.com.mx
MX-07	Hepatology, Hospital General Dr. Manuel Gea Gonzlez, Mexico City	Jacqueline Cordova-Gallardo	jacquiemex2@yahoo.com.mx
MY-01	Universiti Malaya Medical Centre, Kuala Lumpur, Malaysia	Ruveena Rajaram	drruveena81@gmail.com
MY-01	University of Malaya, Kuala Lumpur, Malaysia	Nik Arsyad Nik Muhamad Afendi	nik_arsyad@iium.edu.my
NG-01	Jos University Teaching Hospital Jos, Nigeria	David P Nyam	davidnyampaul@yahoo.com
NG-01	Jos University Teaching Hospital, Jos, Nigeria	Edith N Okeke	edinony@yahoo.com
SD-01	National Center for Gastrointestinal and Liver Disease, Khartoum	Dalia Allam	daloia2244@yahoo.com
SD-01	National Center for Gastrointestinal and Liver Disease, Khartoum	Yashwi Haresh Kumar Patwa	yhpatwa@gmail.com
SG-01	Singapore General Hospital	Hiang Keat Tan	tan.hiang.keat@singhealth.com.sg
SG-01	Singapore General Hospital	Liou Wei Lun	liou.wei.lun@singhealth.com.sg
SG-02	Department of Gastroenterology & Hepatology, Changi General Hospital, Singapore	Wei Ling Danielle Ho	thismustardsheep@gmail.com
SG-02	Department of Gastroenterology &	Yu Jun Wong	wongyujun1985@gmail.com

	Hepatology, Changi General Hospital, Singapore		
TH-01	Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand	Kessarin Thanapirom	tkessarin@hotmail.com
TH-01	Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand	Tongluk Teerasarntipan	kulgnotb@hotmail.com
TR-01	Ankara University, School of Medicine, Ankara	Busra Haktaniyan	busraatmaca13@gmail.com
TR-02	Marmara University School of Medicine, Istanbul	Feyza Gunduz	drfgunduz@yahoo.com
TR-02	Marmara University School of Medicine, Istanbul	Rahmi Aslan	rahmiaslan@yahoo.com
TR-03	Gaziantep University School of Medicine, Gaziantep	Abdullah Emre Yildirim	draemreyildirim@gmail.com
TR-03	Gaziantep University School of Medicine, Gaziantep	Sezgin Barutcu	sezginbarutcu@hotmail.com
TR-04	Ege University School of Medicine, Izmir	Alper Uysal	alper_uysal@live.com
TR-04	Ege University School of Medicine, Izmir	Zeki Karasu	zekikarasu@gmail.com
TR-05	Mersin University School of Medicine, Mersin	Enver Ucbilek	enucbilek@hotmail.com
TR-05	Mersin University School of Medicine, Mersin	Tolga Kosay	tolgakosay@hotmail.com
TR-06	Akdeniz University School of Medicine, Antalya	Dinç Dinçer	Dinc@akdeniz.edu.tr
TR-06	Akdeniz University School of Medicine, Antalya	Haydar Adanır	haydaradanir@hotmail.com
US-01	Virginia Commonwealth University, Richmond	Somaya Albhaisi	somaya.albhaisi@vcuhealth.org
US-03	Baylor University Medical Center, Dallas	Mohammad Amin Fallahadeh	aminfa91@gmail.com
US-03	Baylor University Medical Center, Dallas	Sumeet Asrani	asrani.sumeet@bswhealth.org
US-15	University of Pennsylvania	K Rajender Reddy	reddyr@pennmedicine.upenn.edu
US-17	Richmond VA Medical Center	Jawaid Shaw	jawaidshaw@gmail.com
US-24	Mayo Clinic, Scottsdale	Hugo Vargas	vargas.hugo@mayo.edu
US-28	University of Washington	Natalia Filipek	nfilipek@uw.edu
US-28	University of Washington	Scott W Biggins	bigginssw@upmc.edu
US-31	Mercy Medical Center, Baltimore	Paul Thuluvath	thuluvath@gmail.com
US-31	Mercy Medical Centre, Baltimore	Somya Sheshadri	sshesadri@gmail.com
US-32	Duke University	Kara Wegermann	kara.wegermann@duke.edu
US-32	Duke University	Matthew Kappus	matthew.kappus@duke.edu
US-33	Mayo Clinic, Jacksonville	Andrew Keaveny	keaveny.andrew@mayo.edu
US-34	University of Pittsburgh	Andres Duarte Rojo	Andres.Duarte@northwestern.edu
US-34	University of Pittsburgh	Ricardo Cabello Negrillo	ricardo.cabello@innova.org
US-35	Columbia University Medical Center	Elizabeth Verna	ev77@cumc.columbia.edu

Supplementary reference

1. Hosmer Jr. DW, Lemeshow S, Sturdivant RX. Applied Logistic Regression. Hoboken, NJ: John Wiley & Sons; 2013