Appendix:

Data:

Statistical analysis:

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

Inpatient Mortality: Age, Male Sex, Portal Vein Thrombosis, Diabetes, Hypertension, Hyperlipidemia, Prior Variceal Bleed, Prior HE, Prior Ascites, Prior Large Volume Paracentesis, Prior Hydrothorax, Prior AKI, Prior Hepatorenal Syndrome, Prior AKI, Prior Hepatorenal Syndrome, Prior Hyponatremia, Prior HCC, 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 for hepatitis B, Infections at Admission or within the first 48 Hours, Liver Related Admission, Admission MELD-Na, Alcohol-related etiology, Viral etiology, World Bank Income Group

30-Day Mortality: Age, Male Sex, Portal Vein Thrombosis, Diabetes, Hypertension, Hyperlipidemia, Prior Variceal Bleed, Prior HE, Prior Ascites, Prior Large Volume Paracentesis, Prior Hydrothorax, Prior AKI, Prior Hepatorenal Syndrome, Prior AKI, Prior Hepatorenal Syndrome, Prior Hyponatremia, Prior HCC, 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 for hepatitis B, Infections at Admission or within the first 48 Hours, Liver Related Admission, Nosocomial Infections, Discharge MELD-Na, Hospital AKI, ICU Transfer, Brain Failure, Respiratory Failure, Circulatory Failure, Alcohol-related etiology, Viral etiology, World Bank Income Group

In-Hospital Transplant: Age, Male Sex, Portal Vein Thrombosis, Diabetes, Hypertension, Hyperlipidemia, Prior Variceal Bleed, Prior HE, Prior Ascites, Prior Large Volume Paracentesis, Prior Hydrothorax, Prior AKI, Prior Hepatorenal Syndrome, Prior AKI, Prior Hepatorenal Syndrome, Prior Hyponatremia, Prior HCC, 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 for hepatitis B, Infections at Admission or within the first 48 Hours, Liver Related Admission, Admission MELD-Na, Alcohol-related etiology, Viral etiology, World Bank Income Group

30-Day Transplant: Age, Male Sex, Portal Vein Thrombosis, Diabetes, Hypertension, Hyperlipidemia, Prior Variceal Bleed, Prior HE, Prior Ascites, Prior Large Volume Paracentesis, Prior Hydrothorax, Prior AKI, Prior Hepatorenal Syndrome, Prior AKI, Prior Hepatorenal Syndrome, Prior Hyponatremia, Prior HCC, 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 for hepatitis B, Infections at Admission or within the first 48 Hours, Liver Related

Admission, Discharge MELD-Na, Alcohol-related etiology, Viral etiology, World Bank Income Group

Linearity assumption testing:

The linearity assumption was assessed by dividing the continuous variables (Age, MELD-Na) into five groups and then fit with these groups as categorical variables (factors). The resulting parameter estimates for the parameter estimates were then plotted to see if they appeared to be linear. In addition, a likelihood ratio test was performed to assess if the variables could be treated as linear as opposed to categorical; the resulting likelihood ratio test indicated that the simpler model (continuous as opposed to categorical) was preferred. Finally, the Hosmer-Lemeshow test did not indicate any lack of fit and thus no additional complexity to the model was need. Given these multiple assessments of the linearity assumption, we were confident that the models are linear in the log-odds as required by the model.

Definitions of Kidney dysfunction:

Stage 2: Increase in serum creatinine ≥2.0-3.0 times from baseline

Stage 3: Increase in serum creatinine ≥3.0 times from baseline OR Serum creatinine 4.0mg/dl with an acute increase of 0.3 mg/dl OR Initiation of renal replacement therapy

Stage of Hepatic Encephalopathy according to West-Haven criteria:

Stage 1: Changes in behavior with minimal change in level of consciousness

Stage 2: Gross disorientation, drowsiness, possibly asterixis, inappropriate behavior

Stage 3: Marked confusion, incoherent speech, sleeping most of the time but arousable to vocal stimuli

Stage 4: Comatose, unresponsive to pain; decorticate or decerebrate posturing

Definitions of Infections:

(a) spontaneous bacteremia: positive blood cultures without a source of infection, (b) SBP: ascitic fluid polymorphonuclear cells >250/μL with/without a positive fluid culture, (c) lower respiratory tract infections: new pulmonary infiltrate in the presence of: (i) at least one respiratory symptom (cough, sputum production, dyspnea, pleuritic pain) with (ii) at least one finding on auscultation (rales or crepitation) or one sign of infection (core body temperature >38°C or < 36 °C, shivering or leucocyte count >10,000/mm^3 or <4,000/mm^3) in the absence of antibiotics, (d) *Clostridium difficile*: diarrhea with a positive *C. difficile* assay (e) bacterial entero-colitis: diarrhea or dysentery with a positive stool culture for *Salmonella, Shigella, Yersinia, Campylobacter, or* pathogenic *E. coli*, (f) skin infection: fever with cellulitis, (g) urinary tract infection (UTI): urine WBC >15/high power field with either positive urine gram stain or culture in a symptomatic patient, (h) intra-abdominal infections: diverticulitis, appendicitis, cholangitis, etc., (i) secondary bacterial peritonitis: >250 polymorphonuclear cells/μL of ascitic fluid in the presence of an intra-abdominal source of peritonitis and multiple organisms cultured from ascitic fluid.

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Table S2: Center and region-wise breakdown of subjects enrolled

Center name	Region	Country	World Bank Classification	Number enrolled
CHU de Cocody	Africa	Cote d'Ivoire	Lower middle income	50
Ibn Sina Hospital	Africa	Sudan	Low income	33
Jos University	Africa	Nigeria	Lower middle income	31
Maputo Central Hospital	Africa	Mozambique	Low income	3
Mustapha University Hospital	Africa	Algeria	Lower middle income	50
St. Paul's Hospital Millennium Medical College	Africa	Ethiopia	Low income	49
All India Institute of Medical Sciences	Asia	India	Lower middle income	50
Apollo Hospitals	Asia	India	Lower middle income	17
Asian Institute of Gastroenterology	Asia	India	Lower middle income	50
Beijing Youan Hospital, Capital Medical University	Asia	China	Upper middle income	50
CMC Vellore	Asia	India	Lower middle income	50
Chongyi Second	Asia	China	Upper middle income	49
Hong Kong University	Asia	Hong Kong SAR, China	High Income	50
ILBS Hospital Delhi	Asia	India	Lower middle income	33
Jaslok Hospital	Asia	India	Lower middle income	50
KIMS Bhubaneswar	Asia	India	Lower middle income	49
King Chulalongkorn Memorial Hospital	Asia	Thailand	Upper middle income	49
Mengchao Hepatobiliary Hospital of Fujian Medical University	Asia	China	Upper middle income	50
Nanfang Hospital, Southern Medical University	Asia	China	Upper middle income	44
PGIMER Chandigarh	Asia	India	Lower middle income	50
Rela Institute	Asia	India	Lower middle income	50
Ren Ji Hospital, Shanghai Jiao Tong University	Asia	China	Upper middle income	44
Ruijin Hospital	Asia	China	Upper middle income	47
Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow	Asia	India	Lower middle income	50
Second Hospital of Shandong University	Asia	China	Upper middle income	38
Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine	Asia	China	Upper middle income	49
Singapore General	Asia	Singapore	High income	50
Sir Ganga Ram Hospital	Asia	India	Lower middle income	49

The Fifth People's Hospital of Suzhou	Asia	China	Upper middle income	50
The First Affiliated Hospital of Guangxi Medical University	Asia	China	Upper middle income	48
The First Affiliated Hospital of Wenzhou Medical University	Asia	China	Upper middle income	49
The First Hospital of Jilin University	Asia	China	Upper middle income	50
The Second XiangYa Hospital of Central South University	Asia	China	Upper middle income	50
The Third Affiliated Hospital of Hebei Medical University	Asia	China	Upper middle income	50
The Third Affiliated Hospital of Sun Yat-sen University	Asia	China	Upper middle income	36
The Third People's Hospital of Guilin	Asia	China	Upper middle income	45
Union Hospital, Tongji Medical College, Huazhong University of Science and Technology	Asia	China	Upper middle income	49
University of Malaya Medical Centre	Asia	Malaysia	Upper middle income	50
West China Hospital of Sichuan University	Asia	China	Upper middle income	43
Zhongshan Hospital, Fudan University	Asia	China	Upper middle income	46
Glasgow Royal Infirmary	Europe	United Kingdom	High income	44
Hippokration General Hospital, Athens	Europe	Greece	High income	8
Nottingham	Europe	United Kingdom	High income	50
Queen Elizabeth Hospital Birmingham	Europe	United Kingdom	High income	50
Royal Berkshire Hospital	Europe	United Kingdom	High income	50
Royal Infirmary of Edinburgh	Europe	United Kingdom	High income	27
UMC Freiburg	Europe	Germany	High income	28
Akdeniz University	Middle East	Turkey	Upper middle income	50
Cleveland Clinic Abu Dhabi	Middle East	United Arab Emirates	High income	49
Ege University	Middle East	Turkey	Upper middle income	50
Gaziantep University	Middle East	Turkey	Upper middle income	43
Marmara University	Middle East	Turkey	Upper middle income	50
Mersin University	Middle East	Turkey	Upper middle income	40
Tel Aviv Sourasky Medical Center	Middle East	Israel	High income	41
Ankara University	Middle East	Turkey	Upper middle income	48

Baylor University Medical Center Dallas	North America	United States	High income	50
Centro Medico Nacional La Raza	North America	Mexico	Upper middle income	50
Centro Mexico	North America	Mexico	Upper middle income	50
Columbia University Medical Center	North America	United States	High income	18
Duke University	North America	United States	High income	25
Health Sciences Centre, Manitoba	North America	Canada	High income	44
Hospital Civil de Guadalajara Fray Antonio Alcalde	North America	Mexico	Upper middle income	50
Hospital General	North America	Mexico	Upper middle income	47
Hospital General Dr. Manuel Gea Gonzalez	North America	Mexico	Upper middle income	50
Instituto Nacional	North America	Mexico	Upper middle income	50
Instituto de Salud Digestiva	North America	Mexico	Upper middle income	50
Mayo Clinic - Jacksonville	North America	United States	High income	50
Mayo Clinic - Scottsdale	North America	United States	High income	50
Mayo Rochester	North America	United States	High income	49
Mercy Medical Center	North America	United States	High income	49
Richmond VAMC	North America	United States	High income	48
University of Toronto	North America	Canada	High income	50
University of Alberta	North America	Canada	High income	50
University of Pennsylvania	North America	United States	High income	50
University of Pittsburgh	North America	United States	High income	50
University of Washington	North America	United States	High income	50
Virginia Commonwealth University	North America	United States	High income	50
Prince of Wales Hospital	Oceania	Australia	High income	50
John Hunter Hospital	Oceania	Australia	High income	50
Royal North Shore Hospital	Oceania	Australia	High income	16
Royal Perth Hospital	Oceania	Australia	High income	50
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St George Liver Clinic	Oceania	Australia	High income	27
Westmead Hospital	Oceania	Australia	High income	49
Hospital Britanico de Buenos Aires	South America	Argentina	Upper middle income	4
Hospital Federal de Bonsucesso	South America	Brazil	Upper middle income	16
Hospital Italiano	South America	Argentina	Upper middle income	50

Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo	South America	Brazil	Upper middle income	50
Hospital de Clinicas de Porto Alegre	South America	Brazil	Upper middle income	23
Pontificia Universidad Catolica de Chile	South America	Chile	High income	37

Table S3: Reasons for admission depending on country of origin

	L/LMIC	UMIC	HIC	*p*-value
Liver Related Admission	94% (672)	94% (1653)	85% (1202)	<0.0001
Liver Related Reason				
GI Bleed	34% (227)	21% (354)	25% (306)	<0.0001
Hepatic Encephalopathy	40% (269)	25% (407)	32% (380)	<0.0001
Electrolyte disorders	32% (213)	18% (293)	26% (313)	<0.0001
Acute kidney injury	30% (201)	17% (282)	29% (349)	<0.0001
Anasarca	33% (222)	41% (672)	35% (417)	0.0002
HBV Flare	4% (24)	2% (192)	1% (8)	<0.0001
Drug-induced liver injury	6% (41)	2% (30)	0% (5)	<0.0001
Infection Admission	26% (188)	21% (362)	19% (275)	<0.0001
Spontaneous bacterial peritonitis	35% (107)	28% (151)	23% (91)	0.0008
Spontaneous Bacteremia	8% (24)	6% (32)	8% (33)	0.3220
Respiratory tract infection	15% (46)	20% (111)	14% (57)	0.0247
Skin and soft-tissue Infection	6% (17)	5% (25)	8% (33)	0.0674
Urinary tract infection	14% (43)	14% (76)	16% (65)	0.6263
Clostridioides Difficile	0% (0)	1% (3)	2% (9)	0.0059
Bacterial Enterocolitis	1% (3)	1% (4)	1% (3)	0.9219
Intra-abdominal Infections	2% (5)	8% (45)	6% (24)	0.0005
Fungal Infection	2% (6)	1% (4)	1% (2)	0.1604
Secondary Bacterial Peritonitis	1% (2)	1% (6)	1% (3)	0.7971
Procedure-Related Infection	1% (3)	1%(5)	2% (8)	0.3102
Other	9% (27)	8% (46)	14% (55)	0.0232
Liver unrelated Admission	2% (17)	3% (56)	10% (147)	<0.0001
Cardiac	18% (3)	7% (4)	11% (16)	0.4439
Respiratory	6% (1)	11% (6)	13% (19)	0.6659
Psychiatric	0% (0)	5% (3)	6% (9)	0.8938
Orthopedic	6% (1)	11% (6)	7% (10)	0.7113

L/LMIC: lower and lower middle income country, UMIC: upper middle income country and HIC: high income country.

Table S4: Multi-variable analysis for Inpatient and 30-day mortality

Inpatient mortality			**30-day Mortality**		
Variable	p-value	OR (95% CI)	Variable	p-value	OR (95% CI)
Age	<0.0001	1.02 (1.01, 1.03)	Age	<0.0001	1.04 (1.03, 1.05)
Prior HCC	0.0111	1.86 (1.16, 3.00)	Prior Ascites	0.0039	1.57 (1.16, 2.12)
Transplant Listing	0.0104	0.61 (0.41, 0.89)	Prior HCC	0.0136	1.94 (1.15, 3.27)
Prior 6 Month Hospitalization	0.0066	0.70 (0.54, 0.91)	Transplant Listing	0.0041	0.52 (0.33, 0.81)
Prior 6 Month Infections	0.0174	1.43 (1.07, 1.92)	Admission Rifaximin	0.0177	0.69 (0.51, 0.94)
Admission Lactulose	0.0008	1.56 (1.20, 2.02)	Infection Admission	0.0028	1.51 (1.15, 1.97)
Admission Diuretics	0.0385	0.78 (0.61, 0.99)	Discharge MELD-Na	<0.0001	1.18 (1.16, 1.20)
Admission SBP Prophylaxis	0.0047	0.61 (0.43, 0.86)	Hospital AKI	<0.0001	2.07 (1.56, 2.76)
Admission HBV Antivirals	0.0001	0.46 (0.31, 0.68)	Grade 3-4 HE	<0.0001	2.52 (1.80, 3.54)
Infection Admission	<0.0001	2.38 (1.89, 3.01)	Ventilation	<0.0001	3.60 (2.36, 5.48)
MELD-Na admission	<0.0001	1.14 (1.12, 1.15)	Vasopressor use	<0.0001	3.38 (2.32, 4.91)
World Bank Group	<0.0001		World Bank Group	<0.0001	
LMIC vs High		2.54 (1.82, 3.54)	LMIC vs High		1.84 (1.24, 2.72)
UMIC vs High		2.14 (1.61, 2.84)	UMIC vs High		1.95 (1.44, 2.65)

L/LMIC: lower and lower middle income country, UMIC: upper middle income country and HIC: high income country, HCC: hepatocellular cancer, AKI: acute kidney injury, HE: hepatic encephalopathy, SBP: spontaneous bacterial peritonitis, MELD-Na: model for end-stage liver disease sodium

Table S5: Multi-variable analysis for Inpatient and 30-day liver transplant

Inpatient Liver Transplant			30-day Liver Transplant		
Variable	p-value	OR (95% CI)	Variable	p-value	OR (95% CI)
Transplant Listing	<0.0001	10.01 (6.29, 15.94)	Age	<0.0001	0.97 (0.95, 0.98)
Hepatorenal Syndrome	0.0096	2.09 (1.20, 3.65)	Transplant Listing	<0.0001	8.40 (5.88, 12.01)
Admission Lactulose	0.0319	1.75 (1.05, 2.91)	Hepatorenal Syndrome	<0.0001	2.83 (1.76, 4.55)
MELD-Na	<0.0001	1.15 (1.11, 1.19)	Prior Hyponatremia	<0.0001	2.64 (1.84, 3.80)
Diabetes	0.0224	1.77 (1.08, 2.89)	Prior Ascites	0.0058	2.11 (1.24, 3.58)
Age	0.0299	0.98 (0.96, 1.00)	Admission Lactulose	0.0004	2.01 (1.37, 2.94)
			Liver Related Admission	0.0289	2.21 (1.09, 4.51)
World Bank Group LMIC vs High UMIC vs High	<0.0001	 0.21 (0.10, 0.41) 0.41 (0.24, 0.69)	World Bank Group LMIC vs High UMIC vs High	<0.0001	 0.21 (0.11, 0.40) 0.58 (0.39, 0.85)

L/LMIC: lower and lower middle income country, UMIC: upper middle income country and HIC: high income country, MELD-Na: model for end-stage liver disease sodium

CLEARED Site Characterization Survey 1

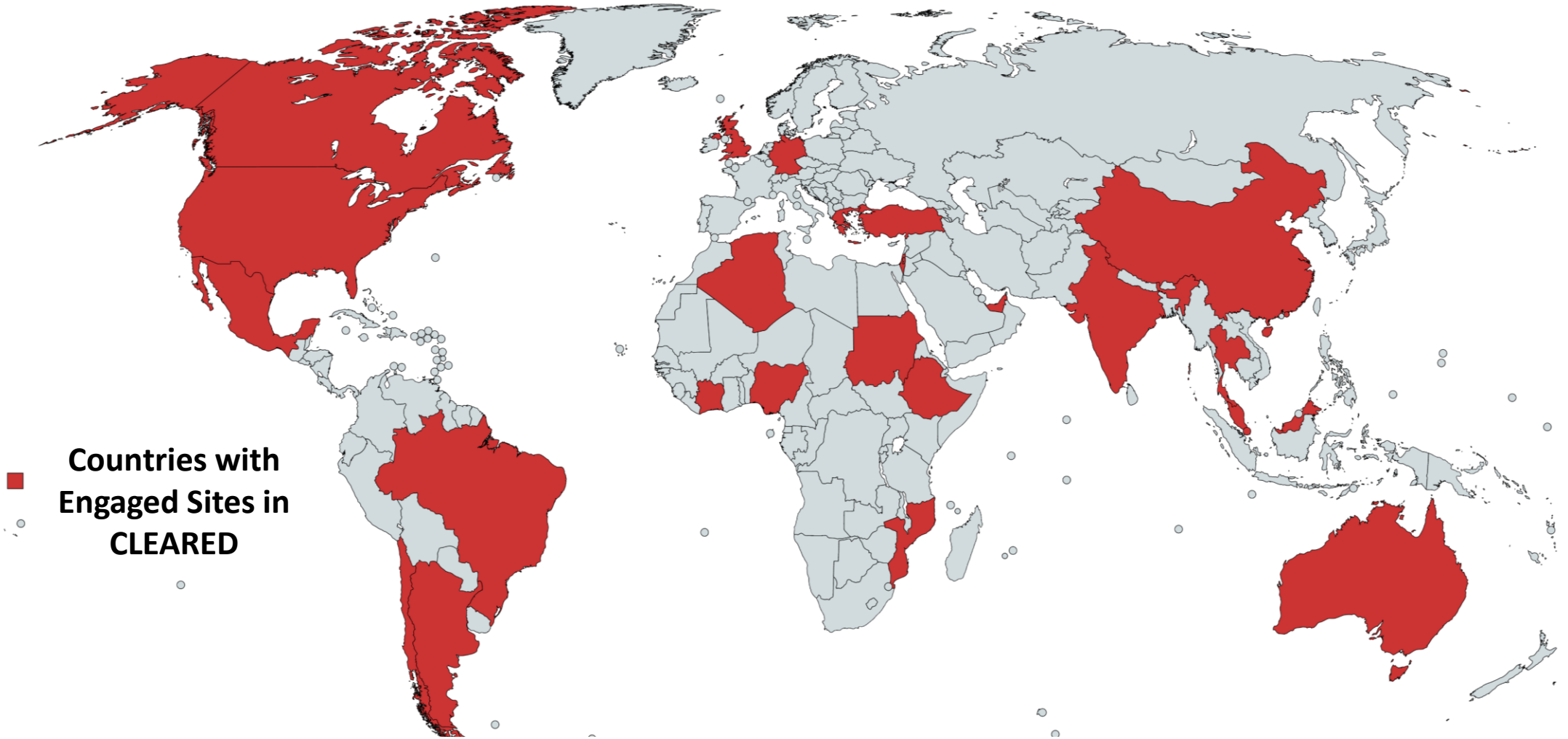
Please complete the survey below to help us characterize your site ([site_id] [site_name]). Answer this for the general patient population you encounter in your practice, *not* the specific patients enrolled in the CLEARED project.

Thank you!

What percentage of your patients have health insurance?	◯ 0-25%, ◯ 26-50% ◯ 51-75% ◯ 76-100%
What is the most prominent type of insurance at your site?	◯ National insurance ◯ Private ◯ Military or Veteran ◯ Other
Other type of insurance:	_____
Is liver transplantation available in your hospital?	◯ Yes ◯ No
Is liver transplantation available in your country?	◯ Yes ◯ No
What percentage of your patients can afford to pay for liver transplantation?	◯ 0-25%, ◯ 26-50% ◯ 51-75% ◯ 76-100%
Is there a medical ICU in your hospital?	◯ Yes ◯ No
How many beds are in your hospital's ICU?	_____
What percentage of your patients can afford to pay for ICU care?	◯ 0-25%, ◯ 26-50% ◯ 51-75% ◯ 76-100%
Does your hospital offer emergency (nighttime and weekend) upper GI endoscopy for patients with GI hemorrhage?	◯ Yes ◯ No
What percentage of your patients forgo medically indicated tests and/or treatments for financial reasons?	◯ 0-25%, ◯ 26-50% ◯ 51-75% ◯ 76-100%
Do you have rifaximin in your country?	◯ Yes ◯ No

What percentage of your patients can afford to pay for rifaximin?	◯ 0-25%, ◯ 26-50% ◯ 51-75% ◯ 76-100%
Do you have terlipressin in your country?	◯ Yes ◯ No
What percentage of your patients can afford to pay for terlipressin?	◯ 0-25%, ◯ 26-50% ◯ 51-75% ◯ 76-100%
Do you have somatostatin or octreotide in your country?	◯ Yes ◯ No
What percentage of your patients can afford to pay for somatostatin or octreotide?	◯ 0-25%, ◯ 26-50% ◯ 51-75% ◯ 76-100%
What percentage of your patients can afford to pay for IV albumin?	◯ 0-25%, ◯ 26-50% ◯ 51-75% ◯ 76-100%
Is there a hospice or palliative care program available to your patients?	◯ Yes ◯ No
What percentage of your patients can afford to pay for hospice/palliative care?	◯ 0-25%, ◯ 26-50% ◯ 51-75% ◯ 76-100%

Figure S1



Chronic Liver disease Evolution And Registry for Event and Decompensation (CLEARED) Global Study of Liver Disease Outcomes in Inpatients

PIs: Jasmohan Bajaj and Ashok Choudhury
Multiple sites in USA, India, China, Canada, Brazil, Mexico, Turkey, Korea and others

Protocol Date: 18 Mar 2021

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Background

There is a need to determine the predictors of complications and mortality in patients with chronic liver disease worldwide. Currently several definitions of ACLF that do not cross-reference with each other are being used. This has hindered the development of uniform diagnostic criteria and reduced the ability to generalize findings. Patients with chronic liver disease (F3 or higher, or FIB-4>1.45 https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4) and cirrhosis both need to be evaluated for 30-day and 90-day outcomes with precipitation based on hepatic or extrahepatic insults. These patients will need to be followed for inpatient, at 30-day and at 90-day outcomes, including complications which need to be differentiated from the precipitants that brought the patients in to the hospital. The goal is to define parameters of mortality, infections, organ failures and complications agnostic of currently available definitions such as APASL, EASL-CLIF, NASCELD or Chinese Society of Hepatology or other national societies.

Overarching objective

Determine predictors of inpatient mortality and other complications in patients with cirrhosis agnostic of pre-formed definitions of ACLF around the world.

Population

Multi-center study across ~100 sites worldwide.

Subject characteristics

Inpatients with chronic liver disease and/or cirrhosis.

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. Post-TIPS if TIPS is >6 months prior
9. Known recent MI (<6 months) or stroke with residual defects

DATA COLLECTION

Following ethics approval, consecutive eligible subjects with cirrhosis (maximum 50 per site), presenting to inpatient wards at each participating institution, will be approached for participation in the study. Consent will be obtained from the patient or the legally authorized representative if the patient is unable to consent (hepatic encephalopathy, intubated etc.) as per local regulations. After consent is signed, the rest of the data will be collected through chart review. Medical records will be reviewed for the details during the hospitalization until day 30 and day 90 (optional) from the date of hospital discharge. For practical purposes, the 30 and 90 days will start from the date of discharge from the current hospital (regardless of whether transferred from another hospital).

All data will be entered in a de-identified excel sheet and data captured will include the following data:

- Demographics (age, sex, etiology of cirrhosis, years since diagnosis of cirrhosis made)
- Degree of liver dysfunction (Child-Pugh, MELD-Na for those with cirrhosis, FIB-4 values), renal function, electrolytes
- Current admission –does patient have compensated or decompensated cirrhosis,

- Compensated / decompensated cirrhosis based on data within 6 months of this admission.

- If decompensated, form(s) of decompensation (ascites, hydrothorax, variceal bleed, hepatic encephalopathy, coagulopathy) and other complications (Spontaneous bacterial peritonitis (SBP), Hepato-renal syndrome) and HCC
- Whether the current episode of decompensation is the index episode or subsequent episode; if subsequent episode, the time period between the two episodes of decompensation.
- Current medications and reason for initiation for rifaximin, beta-blockers, statins, and acid suppressive agents
- Vitals signs and lab values on admission
- Details of infections including site, type, organism, antibiotic used, number of infections, length of stay, ICU stay and outcomes and details of other complications of cirrhosis
- If transplant happened, time to liver transplant
- 90-day outcome (if alive, transplanted, in a hospice, or deceased)

Confirmed infections: those with the following characteristics:

1. **Spontaneous bacteremia:** *positive blood cultures* in the absence of any recognized source of infection
2. **Spontaneous Bacterial Peritonitis (SBP)**: 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

Primary Endpoint

Mortality at 30 days after discharge.

Secondary Endpoints

1. Complications during hospitalizations
2. ICU transfer
3. Transplantation or withdrawal from candidacy
4. Organ failures
5. Infections (at baseline, nosocomial infections, second infections) and their organisms
6. Mortality at 90 days after discharge (optional to be determined by site PI)

Risks

This is an observational study that has a low degree of risk. Potential risk include the following:

- Privacy and Confidentiality: Minor risk of breach of confidentiality

Risk Reduction

All study data and will be stored without identifiers in a secure (locked) location and only authorized study personnel will have access to study records. Only de-identified data will be sent for combined analysis.

Monitoring & Reporting of Adverse Events

This is an observational and data collection study. Subjects do not receive treatment for any medical condition as part of this study and none of the outcomes over 30 days will be considered adverse or serious adverse events.

Subject Compensation

Participants will not be paid for their participation in the study.

Data Collection

Data collection sheets are attached and detail study data to be collected. The professionally managed Microsoft OneDrive implementation at the VCU Health System will be used for data collection and movement, providing encryption in transit and at rest. Data collected for the central data repository will be de-identified, minimizing the risk to participants. No personal information will be stored or revealed between sites. Data access will be limited per individual using the principle of least privilege, in accordance with steering committee guidance.

Risk/Benefit Assessment

Patients with cirrhosis are at a high risk of mortality, especially due to infections and other complications. Currently there are imperfect strategies for predicting their occurrence and outcomes. There are several recent retrospective studies suggesting that in addition to the severity of liver disease, medication use (acid suppression, beta-blockers and rifaximin) can be significant factors in either predisposing or protecting cirrhotic subjects from infections. This multi-center data collection study is planned to answer these questions prospectively as part of a natural history of mortality and other negative outcomes in cirrhosis. This will lend a unique insight into the role of these medications in the occurrence of infections and will also allow design intervention trials in the future

Data Analysis Plan

Descriptive statistics will be applied to all parameters collected. Subjects will be divided into those with and without beta-blockers, acid suppressive and

rifaximin, statin use at the time of admission and they will be compared to those who were not on those medications. We will compare the determinants of transplant-free survival and death at 30 days based on complications, precipitants (including infections) and their management in the entire group as well as evaluating regional variations in survival. The results of the subjects will be compared using ANOVA for continuous variables, and Chi square test for nominal variables. Subjects who receive a transplant will be censored. A p value of <0.05 will be regarded as statistically significant. Comparisons will be done between:

A. Compensated cirrhosis vs re-compensated vs. decompensated cirrhosis prior to hospitalization
B. Extra-hepatic precipitant vs intra-hepatic precipitant
C. Infected versus not on admission versus development (on admission vs. nosocomial vs. second infection)