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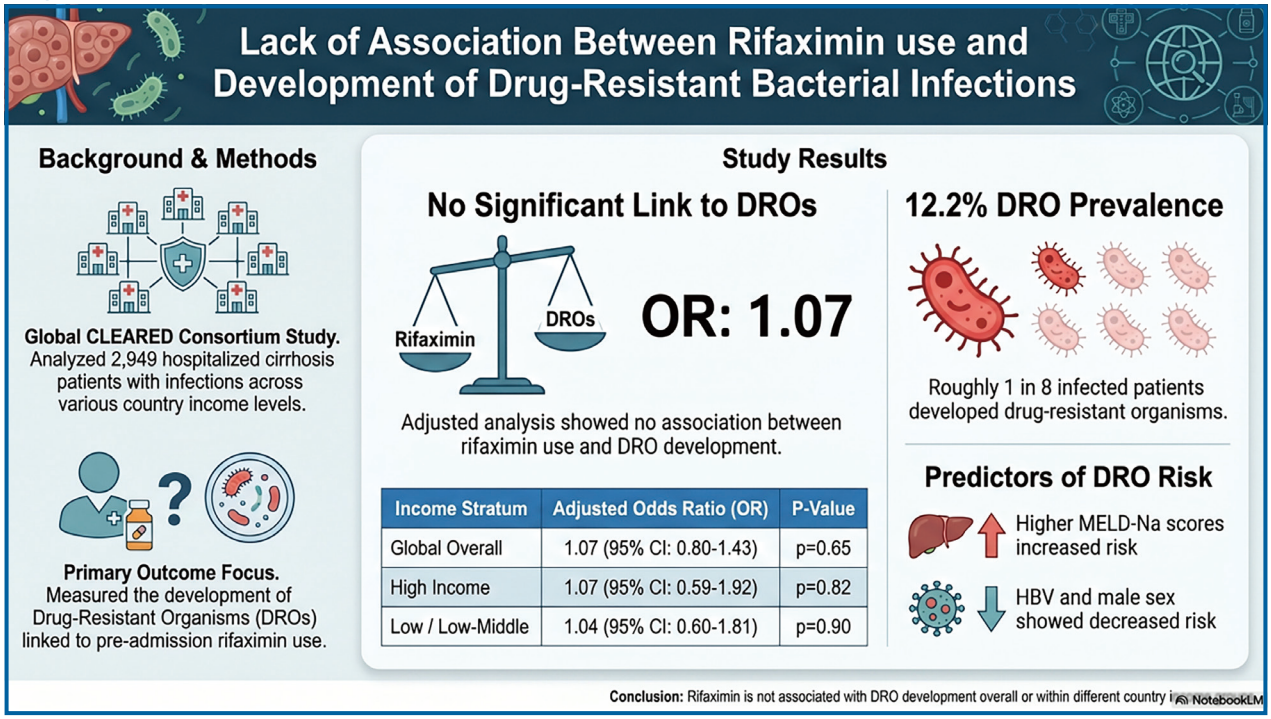
Original Article

Lack of association between rifaximin and drug-resistant infections: a global multicenter inpatient cirrhosis cohort

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Graphical Abstract



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Study Highlights

- Bullet point 1: Rifaximin is useful to prevent HE recurrence in cirrhosis.Recent pre-clinical analysis showed antimicrobial resistance emergence with rifaximin, but the clinical relevance is unclear.
- Bullet point 2: Analyzing 2949 cirrhosis patients hospitalized with infections in the global CLEARED Consortium across high/middle/low-income countries, DRO were found in 12.2% overall and in 24% of culture-positive infections, which increased mortality.
- Bullet point 3: 29% were on rifaximin, which did not affect the presence of DROs overall or within country-income strata on multi-variable analysis. Pre-clinical resistance emergence to rifaximin is likely a reflection of advanced cirrhosis and unlikely to be associated with DRO infections.

Background/Aims: Infections with drug-resistant organisms (DROs) are associated with poor outcomes in cirrhosis. Rifaximin, widely used for hepatic encephalopathy (HE), could promote cross-resistance, but data regarding clinical impact are conflicting. Aim: Determine predictors of DROs in a global cirrhosis inpatient cohort focusing on pre-admission rifaximin use.

Methods: From the global CLEARED consortium, we focused on cirrhosis inpatients with infections on/during admission. Clinical/demographic/medication, especially rifaximin details were recorded. The primary outcome was DRO development. Multivariable regression for DRO including clinical, medications, and country income was performed.

Results: 2,949 infected inpatients (55.3 years, 62.9% male) were included. 12.2% of all and 24.4% of culture-positive infections developed DROs; these patients had higher HE (39 vs. 31%, *P*=0.003), hepatorenal syndrome (25 vs. 19%, *P*=0.006), lactulose (55 vs. 47%, *P*=0.008) and rifaximin use (34 vs. 27%, *P*=0.006) on crude comparisons but country-income distributions were similar. 29.7% were on pre-admission rifaximin, mostly HE-related; they had more advanced cirrhosis and from low/low-middle-income countries. Daptomycin was used in 1.5%, linked with DROs (5.0 vs. 1.0%, *P*<0.0001) without a difference in rifaximin use (1.4 vs.1.7%, *P*=0.61). On adjusted analysis, MELD-Na (1.03, 95% CI 1.02–1.04, *P*<0.001) increased, whereas male sex (0.73, 95% CI 0.58–0.92, *P*=0.008) and hepatitis-B (0.65, 95% CI 0.45–0.92, *P*=0.020) decreased DRO. Rifaximin was not associated with DROs overall (OR 1.07, 95% CI 0.80–1.43, *P*=0.65) or within income strata (high: 1.07, 95% CI 0.59–1.92, *P*=0.82, upper-middle: 1.18, 95% CI 0.74–1.85, *P*=0.49, low/low-middle: 1.04, 95% CI 0.60–1.81, *P*=0.90) despite sensitivity analyses.

Conclusions: In this large global cohort of hospitalized patients with cirrhosis and infections, 12% developed infections involving DROs. 30% had pre-admission rifaximin use which was not linked with daptomycin use or with DRO development on adjusted analysis overall or across country income groups. **(Clin Mol Hepatol 2026;32:1321-1332)**

Keywords: Antibiotic overuse; Disparities; CLEARED consortium; Infections; Daptomycin

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Abbreviations:

AMR, antimicrobial resistance; DRO, drug-resistant organism; HE, hepatic encephalopathy; HIC, high income country; ICU, intensive care unit; IQR, interquartile range; L/LMICs, low/low-middle income countries; MRSA, methicillin-resistant *Staphylococcus aureus;* PSM, propensity score-matched; SBP, spontaneous bacterial peritonitis; SMD, standardized mean difference; UMIC, upper-middle income country; VIF, variance inflation factors

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INTRODUCTION

Patients with cirrhosis are at risk of developing infections, especially with drug-resistant organisms (DROs), which can lead to poor outcomes.[1-3] Acquisition and propagation of DROs is multifactorial and is worsened by the multiple contacts with health care systems, instrumentation, and exposure to antibiotics in patients with cirrhosis.[4] These exposures and resistance patterns vary worldwide and the risk of DRO infections resulting from antibiotic prophylaxis for spontaneous bacterial peritonitis (SBP) has been described.[5-7] A recent study indicated that rifaximin used as treatment for hepatic encephalopathy (HE) causes cross-resistance to daptomycin in vancomycin-resistant *Enterococcus faecium.*[8] However, subsequent analyses have provided conflicting results, which is often complicated using focused database studies and short-term analyses.[9-12] A global cohort that provides perspective considering regional variations and resources would overcome the deficiencies of previous studies. We aimed to determine the predictors of DROs in a global cohort of patients with cirrhosis hospitalized with infections focusing on the relationship of resistant infections, to pre-admission rifaximin use and interaction with daptomycin.

MATERIALS AND METHODS

The CLEARED consortium consists of prospectively enrolled patients with cirrhosis admitted non-electively around the world.[13] Cirrhosis details and history, demographics, initial inpatient course, and country income level using World Bank classifications: high-income countries (HICs), upper-middle-income countries (UMICs), and low- and lower-middle-income countries (L/LMICs) are collected. Inclusion criteria for CLEARED are confirmed cirrhosis, non-elective hospitalizations, and ability to obtain consent. For this manuscript, we only included patients from the CLEARED cohort with confirmed infection on or during admission using standard Infectious Diseases Society of America definitions.[14] We excluded patients admitted electively, those with HIV, COVID-19 or prior transplants or those without any infections. The main outcome was the presence of a DRO, either on admission or during the hospital course; these were defined using standard criteria.[15] We focused on fluoroquinolone resistance, carbapenemase expression, vancomycin resistant enterococci, and methicillin-resistant *Staphylococcus aureus* (MRSA). The secondary outcome was the composite occurrence of either DRO or inpatient death. Other outcomes included death, liver transplant, nosocomial infection, and intensive care unit (ICU) transfer. Details of infections, rifaximin use, and inpatient and 30-day post-discharge course were collected.

Cohort characteristics around time of admission were summarized and compared between the those who were on rifaximin at admission and those who were not (Supplementary Table 1). Similarly, we compared the admission characteristics between those who developed DROs during this admission. Multivariable logistic regression analysis was used to identify the effect of rifaximin on DRO development/composite inpatient death or DRO, adjusting for all other potential confounders that were significantly different between the outcome groups (at $P<0.05$). Multicollinearity was measured using variance inflation factors (VIF) with a cutoff of 5 indicating high correlation between predictors and a cutoff of 2 indicating moderate correlation.[16] Indication (HE, SBP, or neither) for rifaximin and treatment duration (number of months pre-admission that the patient was on rifaximin) were assessed for significance by adding these as predictors into the final multivariable model and assessing their effects. To address heterogeneity that may occur due to differences in country income level, we performed a stratified analysis of income distribution of countries separately.[17]

Multiple sensitivity analyses were conducted to address potential residual confounding that may have occurred when using this model-building approach or to address potential overlap between highly related predictors.

First, we performed a propensity score-matched (PSM) analysis of the cohort, where all variables shown in Tables 1 and 2 (aside from outcomes and DRO-related data) were used to create balanced groups. The R package "MatchIt"[18] was used, with optimal pair matching as the method of choice.[19] The resulting cohort was then compared based on these variables (Supplementary Table 2). We used logistic regression models in the matched cohort to assess the impact of rifaximin on the odds of both outcomes. Finally, we performed a double adjustment,[20] further including variables with $P<0.05$ or standardized mean difference (SMD)>0.1 after matching into multivariable models

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(Supplementary Table 3), which has been shown to remove further confounding that may occur even after PSM.

Secondly, we provided an alternative model-fitting approach that used backwards selection on the full predictor set (not simply those with $P<0.05$), returning parsimonious models for both outcomes. By including all potential predictors, this can identify combinations that may have been omitted when using statistical significance-based approaches alone.

Finally, we refitted the main multivariable models, which contained lactulose on admission & prior HE together, by first omitting lactulose (keeping prior HE in the model), and then the inverse of this (keeping lactulose while removing prior HE).

RESULTS

Of the 8,623 patients in the CLEARED consortium, 2,949 had an infection on or during admission, which was the cohort used for this analysis (Supplementary Fig. 1 and Supplementary Tables 4 and 5). Their mean age was 55.3±13.6 years, with the majority (62.9%) being men and alcohol being the most common cause (42%) of cirrhosis. Of these patients, the majority (54.9%) had an infection on admission, while the remainder had hospital-acquired or post-admission infections. In the six months prior to the index admission, 29.4% were admitted for an infection, and 8.8% had >2 prior infections. The in-hospital mortality rate was 20.4%, 30-days, mortality was 30.0%, 2.9% and 6.6% had liver transplants in-hospital and at 30-days respectively, and 26.6% were transferred to the ICU. The median hospital LOS was 12 days (interquartile range [IQR] 7–20). Almost a third (32.7%) were from high-income, 43% from upper middle and 24% were from low/low-middle income countries.

Rifaximin use characteristics

823 (29.7%) patients were on rifaximin treatment on admission. Most (81%) were on rifaximin for HE, while the remaining were on it for SBP prophylaxis. The majority (87%) were on the 550 mg BID dose, the rest were on th 400 mg TID dosage. The median duration of use (preadmission) was 2 months; 29% were started >6 months prior to admission, while 71% were started within 6 months. Patients on rifaximin were more likely to be younger, male, with alcohol- and MASH-related etiology of cirrhosis, and greater severity of disease, comorbidities and other admission medications suggestive of greater liver disease severity as measured by MELD-Na and cirrhosis history (Table 1). Rifaximin use was highest in L/LMICs and lowest in UMICs.

DRO details

In our analysis cohort, 361 (12.2%) had a DRO present and 837 (28.8%) had the composite outcome of DRO or death. Among the entire cohort, 1,478 had positive cultures (50.1%), of which 494 were gram-positive and 875 were gram-negative (the remainder were non-specified, fungal/viral were not included). This implies that the percentage of DROs represented 24.4% of the culture-positive infections. Specific DRO-related infection types included UTI (30.7%), spontaneous bacteremia (14.9%), respiratory tract infections (14.6%), SBP (13.6%), skin infections (4.9%), intra-abdominal infections (4.6%), and others (16.9%). Among these, women (39.0% *vs*. 24.7%; $P=0.003$) had significantly higher rates of UTI, men had higher rates of SBP (16.7% *vs*. 9.1%; $P=0.04$), and the remainder were not significantly different between genders or were too rare to compare. Of these DROs 13.0% were VRE related, 10% were MRSA related, 29.1% were fluroquinolone related, and 25.8% had carbapenemase resistance, the remainder were unspecified.

Patients with a DRO were and less likely to be male, less likely to have HBV or be on HBV antivirals and were more likely to have MASLD and hyperlipidemia (Table 2). Patients with a DROs also had a worse MELD-Na on admission. These patients also had a higher proportion with history of prior AKI/HRS and HE with medications (lactulose, rifaximin) and a listing for LT. There was a trend towards higher prior infections and admission for infections and higher admission WBC count in those with infections who developed DROs.

Daptomycin use

Only 43 (1.5%) of patients were treated with daptomycin; their median (IQR) age was 59.00 [51.50, 67.50], 58.1% were men, and 46.5% had alcohol-related etiology of cir-

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Table 1. Cohort characteristics split by rifaximin on admission

Characteristic	Overall (n=2,949)	No rifaximin (n=2,126)	On rifaximin (n=823)	*P*-value
Age (yr)	56.00 [46.00, 65.00]	56.00 [46.00, 66.00]	55.00 [45.00, 64.00]	0.026
Male sex	1,854 (62.9)	1,293 (60.8)	561 (68.2)	<0.001
World Bank income group classification				<0.001
High	964 (32.7)	704 (33.1)	260 (31.6)	
Upper middle	1,278 (43.3)	1,062 (50.0)	216 (26.2)	
Low/low-middle	707 (24.0)	360 (16.9)	347 (42.2)	
Etiology				
Alcohol	1,240 (42.0)	856 (40.3)	384 (46.7)	0.002
MASLD	542 (18.4)	358 (16.8)	184 (22.4)	0.001
Hepatitis B	516 (17.5)	433 (20.4)	83 (10.1)	<0.001
Hepatitis C	318 (10.8)	224 (10.5)	94 (11.4)	0.529
Auto-immune liver diseases	174 (5.9)	122 (5.7)	52 (6.3)	0.608
Cryptogenic	220 (7.5)	164 (7.7)	56 (6.8)	0.444
Other	112 (3.8)	84 (4.0)	28 (3.4)	0.554
Comorbidities				
Diabetes	854 (29.0)	583 (27.4)	271 (32.9)	0.004
Hypertension	721 (24.4)	533 (25.1)	188 (22.8)	0.225
Hyperlipidemia	350 (11.9)	252 (11.9)	98 (11.9)	>0.999
Cirrhosis related history				
Prior ascites	2,024 (68.6)	1,352 (63.6)	672 (81.7)	<0.001
Prior variceal bleed	774 (26.2)	492 (23.1)	282 (34.3)	<0.001
Prior hepatic encephalopathy	938 (31.8)	414 (19.5)	524 (63.7)	<0.001
Prior hyponatremia	576 (19.5)	306 (14.4)	270 (32.8)	<0.001
Prior acute kidney injury/HRS	573 (19.4)	302 (14.2)	271 (32.9)	<0.001
Hospitalized in past 6 mo	1,458 (49.4)	959 (45.1)	499 (60.6)	<0.001
Infections in past 6 mo	867 (29.4)	556 (26.2)	311 (37.8)	<0.001
Prior listing for liver transplant	363 (12.3)	191 (9.0)	172 (20.9)	<0.001
Medications on admission				
Β-blockers	958 (32.5)	622 (29.3)	336 (40.8)	<0.001
Diuretics	1,626 (55.1)	1,074 (50.5)	552 (67.1)	<0.001
Lactulose	1,429 (48.5)	698 (32.8)	731 (88.8)	<0.001
SBP prophylaxis	412 (14.0)	199 (9.4)	213 (25.9)	<0.001
Statins	267 (9.1)	191 (9.0)	76 (9.2)	0.888
Proton-pump inhibitors	1,293 (43.8)	814 (38.3)	479 (58.2)	<0.001
HBV antivirals	472 (16.0)	365 (17.2)	107 (13.0)	0.007
Admission reasons				
Infection	1,618 (54.9)	1,125 (52.9)	493 (59.9)	0.001
Liver related	2,553 (86.6)	1,808 (85.0)	745 (90.5)	<0.001
Non-liver related	92 (3.1)	76 (3.6)	16 (1.9)	0.03
Admission labs				
Hemoglobin	10.00 [8.30, 11.71]	10.20 [8.40, 12.00]	9.40 [8.00, 10.97]	<0.001
WBC	7.50 [4.57, 11.80]	7.30 [4.50, 11.60]	8.00 [4.89, 12.50]	0.028
INR	1.61 [1.31, 2.10]	1.55 [1.30, 2.00]	1.82 [1.44, 2.40]	<0.001

Table 1. Continued

Characteristic	Overall (n=2,949)	No rifaximin (n=2,126)	On rifaximin (n=823)	*P*-value
Sodium	134.0 [129.0, 137.9]	134.0 [130.0, 138.0]	132.0 [128.0, 137.0]	<0.001
Creatinine	1.02 [0.71, 1.70]	0.98 [0.70, 1.57]	1.20 [0.80, 1.99]	<0.001
Bilirubin	3.81 [1.58, 10.70]	3.40 [1.41, 9.86]	4.94 [1.95, 12.73]	<0.001
Albumin	2.70 [2.30, 3.20]	2.70 [2.30, 3.20]	2.70 [2.30, 3.10]	0.009
MELD-Na	23.00 [17.00, 29.00]	22.00 [16.00, 28.00]	26.00 [20.00, 32.00]	<0.001
DRO details				
Any DRO	361 (12.2)	238 (11.2)	123 (14.9)	0.006
VRE-related DRO	47 (1.6)	28 (1.3)	19 (2.3)	0.078
MRSA-related DRO	36 (1.2)	26 (1.2)	10 (1.2)	>0.999
Fluoroquinolone DRO	105 (3.6)	76 (3.6)	29 (3.5)	>0.999
Carbapenemase DRO	93 (3.2)	51 (2.4)	42 (5.1)	<0.001
Outcomes				
In-hospital mortality	591 (20.4)	354 (16.9)	237 (29.5)	<0.001
Mortality or hospice discharge	641 (22.1)	399 (19.1)	242 (30.1)	<0.001
In-hospital transplant	82 (2.9)	53 (2.5)	29 (3.7)	0.141
ICU transfer	784 (26.6)	476 (22.4)	308 (37.4)	<0.001
Hospital LOS	12.00 [7.00, 20.00]	12.00 [7.00, 21.00]	11.00 [6.00, 19.50]	0.01
30-Day readmission	562 (29.4)	412 (28.9)	150 (31.1)	0.375
30-Day mortality	745 (30.0)	475 (26.9)	270 (37.7)	<0.001
30-Day transplant	126 (6.6)	78 (5.5)	48 (10.0)	0.001
Composite, death or DRO	837 (28.8)	492 (23.8)	316 (37.7)	<0.001

Values are presented as median [interquartile range] or number (%).
DRO, drug-resistant organism; HBV, hepatitis B virus; HRS, hepatorenal syndrome; ICU, intensive care unit; INR, international normalized ratio; LOS, length of stay; MASLD, metabolic dysfunction associated liver disease; MELD-Na, Model for end-stage liver disease; MRSA, methicillin-resistant *Staphylococcus aureus*; SBP, spontaneous bacterial peritonitis; VRE, vancomycin resistant Enterococcus; WBC, white blood cell count.

rhosis. 58.1% were from HIC *vs*. UMI/L/LMICs which was significantly higher than the percentage of patients not on daptomycin (HIC 32.3%; *P*<0.001). The rate of rifaximin use among these individuals was statistically similar to those not treated with daptomycin (1.4 *vs*. 1.7%; *P*=0.61). Patients on daptomycin had significantly higher DRO emergence (5.0 *vs*. 1.0%; *P*<0.0001), inpatient death (39.5% *vs*. 20.1%; *P*=0.003), and transplant (9.3% *vs*. 2.8%; *P*=0.036) rates, higher 30-day death (48.6% *vs*. 29.7%; *P*=0.021) and transplant (22.7% *vs*. 6.4%; *P*=0.009) rates, longer hospital LOS (median 16 *vs*. 12 days; *P*=0.018), and were more likely to be transferred to the ICU (46.5% *vs*. 26.3%; *P*=0.005). While the number of patients receiving daptomycin was small, a post-hoc sensitivity analysis to determine the smallest difference that could be detected under our study design suggests that our study was powered to detect relatively small absolute differences in exposure rates, supporting the adequacy of the sample size (Supplementary Results).

Multi-variable analysis for DRO development

Variables affecting DRO development included male sex (adj. OR 0.73 [0.58–0.92]; *P*=0.008), HBV etiology (adj. OR 0.65 [0.45–0.92]; *P*=0.020), and higher MELD-Na (adj. OR 1.03 [1.02–1.04]; *P*<0.001). Rifaximin use was not significantly associated with DRO development (adj. OR 1.07 [0.80–1.43]; *P*=0.65) after adjustment for other covariates that significantly differed between the outcome groups (Table 3). Indication and duration of rifaximin therapy did not impact DRO development. Variables affecting the composite outcome of DRO development or death were similar (Table 3). Rifaximin use was not significantly associated with this outcome (adj. OR 1.24 [0.99–1.55], *P*=0.07) after

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Table 2. Cohort characteristics split by DRO development

Characteristic	No DRO (n=2,588)	DRO (n=361)	*P*-value
Age (yr)	56.00 [46.00, 65.00]	55.00 [47.00, 64.00]	0.922
Male sex	1,650 (63.8)	204 (56.5)	0.009
World Bank income group classification			0.418
High	857 (33.1)	107 (29.6)	
Upper middle	1,114 (43.0)	164 (45.4)	
Low/low middle income	617 (23.8)	90 (24.9)	
Etiology			
Alcohol use	1,093 (42.2)	147 (40.7)	0.625
MASLD	463 (17.9)	79 (21.9)	0.078
Hepatitis B	477 (18.4)	39 (10.8)	<0.001
Hepatitis C	289 (11.2)	29 (8.0)	0.088
Auto-immune liver diseases	145 (5.6)	29 (8.0)	0.086
Cryptogenic	190 (7.3)	30 (8.3)	0.583
Other	96 (3.7)	16 (4.4)	0.599
Comorbidities			
Diabetes	737 (28.5)	117 (32.4)	0.139
Hypertension	630 (24.3)	91 (25.2)	0.77
Hyperlipidemia	289 (11.2)	61 (16.9)	0.002
Cirrhosis related history			
Prior ascites	1,776 (68.6)	248 (68.7)	>0.999
Prior variceal bleed	683 (26.4)	91 (25.2)	0.678
Prior overt hepatic encephalopathy	798 (30.8)	140 (38.8)	0.003
Prior hyponatremia	494 (19.1)	82 (22.7)	0.119
Prior acute kidney injury/HRS	483 (18.7)	90 (24.9)	0.006
Hospitalized in past 6 mo	1,266 (48.9)	192 (53.2)	0.143
Infections in past 6 mo	747 (28.9)	120 (33.2)	0.099
Prior listing for liver transplant	305 (11.8)	58 (16.1)	0.025
Medications on admission			
Β-blockers	848 (32.8)	110 (30.5)	0.416
Diuretics	1,423 (55.0)	203 (56.2)	0.696
Lactulose	1,230 (47.5)	199 (55.1)	0.008
Rifaximin	700 (27.0)	123 (34.1)	0.006
SBP prophylaxis	366 (14.1)	46 (12.7)	0.524
Statins	229 (8.8)	38 (10.5)	0.346
Proton-pump inhibitors	1,143 (44.2)	150 (41.6)	0.378
HBV antivirals	442 (17.1)	30 (8.3)	<0.001
Admission reasons			
Infection admission	1,437 (55.5)	181 (50.1)	0.061
Liver related admission	2,243 (86.7)	310 (85.9)	0.739
Non-liver related admission	75 (2.9)	17 (4.7)	0.091
Admission labs			
Hemoglobin	10.00 [8.30, 11.80]	9.60 [8.00, 11.30]	0.012
WBC	7.33 [4.50, 11.62]	8.42 [4.90, 12.90]	0.067

Table 2. Continued

Characteristic	No DRO (n=2,588)	DRO (n=361)	*P*-value
INR	1.60 [1.30, 2.10]	1.80 [1.42, 2.30]	<0.001
Sodium	134.0 [129.0, 138.0]	134.0 [129.0, 137.0]	0.542
Creatinine	1.00 [0.71, 1.66]	1.18 [0.76, 2.00]	0.001
Bilirubin	7.59 (9.08)	9.36 (11.59)	0.001
Albumin	2.75 (0.67)	2.71 (0.69)	0.288
MELD-Na	22.98 (8.27)	25.10 (7.79)	<0.001
Outcomes			
In-hospital mortality	476 (18.7)	115 (32.4)	<0.001
Mortality or hospice discharge	517 (20.3)	124 (34.9)	<0.001
In-hospital transplant	56 (2.2)	26 (7.4)	<0.001
ICU transfer	635 (24.5)	149 (41.3)	<0.001
Hospital LOS	11.00 [7.00, 19.00]	16.00 [9.00, 28.00]	<0.001
30-Day readmission	495 (29.1)	67 (32.4)	0.366
30-Day mortality	606 (28.0)	139 (44.0)	<0.001
30-Day transplant	93 (5.5)	33 (15.6)	<0.001

Values are presented as median [interquartile range] or number (%).
DRO, drug-resistant organism; HBV, hepatitis B virus; HRS, hepatorenal syndrome; ICU, intensive care unit; INR, international normalized ratio; LOS, length of stay; MASLD, metabolic dysfunction associated liver disease; MELD-Na, Model for end-stage liver disease; SBP, spontaneous bacterial peritonitis; WBC, white blood cell count.

Table 3. Multivariable logistic regression model for association with DRO development and composite risk of death/DRO

Variable*	OR (95% CI)	*P*-value
Outcome: DRO development		
Rifaximin on admission	1.07 (0.80–1.43)	0.649
Male sex	0.73 (0.58–0.92)	0.008
HBV etiology	0.65 (0.45–0.92)	0.020
MELD-Na	1.03 (1.01–1.04)	<0.001
Outcome: Composite death or DRO		
Rifaximin on admission	1.24 (0.99–1.55)	0.07
Male sex	0.81 (0.68–0.98)	0.028
HBV etiology	0.59 (0.45–0.76)	<0.001
MELD-Na	1.08 (1.07–1.10)	<0.001

CI, confidence interval; DRO, drug-resistant organism; HBV, hepatitis B virus; MELD-Na, Model for end-stage liver disease; OR, odds ratio.
*Other than admission rifaximin, only variables that are *P*<0.05 on crude comparisons were adjusted for.

covariate adjustment. In all multivariable models, VIF were <2 in all scenarios, indicating an absence of multicollinearity.

Sensitivity analyses

In the propensity-score matched analysis, the matched cohort contained 679 patients per-group (1,358 total). Most variables were adequately balanced, but world bank income level, HBV etiology, prior ascites/VB/hyponatremia/AKI/transplant listing, lactulose, SBPPr, PPI, MELD-Na, and hemoglobin remained significant at *P*<0.05 or had SMD>0.1 (Supplementary Table 2). In the matched cohort, rifaximin usage at admission was not associated with DRO development (*P*=0.758) which persisted after double adjustment (*P*=0.918). The composite outcome of death/DRO was significantly higher in rifaximin patients in the matched cohort (*P*=0.01), but after double adjustment this association was no longer significant (*P*=0.253). A full multivariable model table can be seen in Supplementary Table 3.

Re-fitting models with combinations of prior HE/lactulose did not affect the association between DRO development and rifaximin usage, but in the models that did not have both predictors included (Supplementary Table 6), the composite outcome of inpatient death/DRO became significant.

Finally, using backwards selection to fit the multivariable models did not select rifaximin usage on admission as one of the final predictors included for both outcomes, indicating that this variable did not improve model fit. Specifically,

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the final multivariable model for DRO development contained only HBV etiology and MELD-Na, while the final multivariable model for the composite outcome contained age, income level, HBV etiology, prior ascites/HE/AKI, and MELD-Na.

Subgroup analysis of income level

On subgroup analysis of HICs, UMICs, and L/LMICs separately (Supplementary Table 7), the lack of evidence of association between rifaximin and DRO development persisted. Rifaximin use was not associated with DRO isolation on multi-variable analysis in HIC (adj. OR 1.07 [0.59–1.92]; *P*=0.82), UMIC (adj. OR 1.18 [0.74–1.85]; *P*=0.49), or L/LMICs (adj. OR 1.04 [0.60–1.81]; *P*=0.90). MELD-Na continued to be associated with DRO in UMIC (adj OR 1.05 [1.02–1.07]; *P*<0.001) and L/LMICs (adj OR 1.05 [1.02–1.09]; *P*=0.002). In UMICs only HBV etiology (adj OR 0.50 [0.30–0.80]; *P*=0.005) and male sex (adj OR 0.67 [0.47–0.95]; *P*=0.023) remained significantly associated with DRO emergence. Results were similar for the composite outcome.

DISCUSSION

In a globally representative cohort of prospectively enrolled hospitalized patients with cirrhosis with infections, 12% of total infections and 24% of culture-positive infections were due to DROs. Rifaximin use on admission was seen in almost 30% of patients, who tended to have worse cirrhosis characteristics. On adjusted analysis, rifaximin was not associated with DROs in the entire cohort and within country income levels.

The role of DROs and their prevention in cirrhosis is a critical issue since it can lead to poor outcomes.[6] This was again demonstrated in our cohort where DRO isolation was linked with poor survival and a higher need for liver transplantation. Therefore, identifying endogenous and exogenous sources of DROs is critical to reduce this burden.[4] Prior studies have shown that current/prior antibiotics, hospital exposures, and regional variations play a major role in DRO acquisition.[7,21] Our data show that higher disease severity, prior complications and associated medications such as rifaximin and lactulose, as well as a tendency towards higher infections and hospitalizations within 6 months were associated with DRO isolation. While these are expected in patients with cirrhosis, we aimed to study the impact of rifaximin on DRO development.

Rifaximin is an interesting non-absorbable antibiotic that can reduce ammonia generation even in the germ-free state.[22,23] The important role of rifaximin in HE recurrence prevention has been demonstrated multiple times without any real-world increase in either infections as a whole or DROs in particular.[24-27] Turner et al.[8] performed preclinical and clinical assays showing daptomycin resistance in rifaximin users, but this was not extended towards clinical or DRO-related outcomes. Further studies using databases showed no short-term changes in infections, which were extended by in-depth patient-level analyses of antimicrobial resistance (AMR) genes.[9,11,12] These data, combined with a prior trial of patients before and after rifaximin showed no major increase in AMR genes or resistant infections using rifaximin.[28] A recent TriNetX study showed that patients with cirrhosis who were initiated on HE therapies showed a higher AMR rate and infections in those started on rifaximin versus not.[10] However, databases often suffer from miscoding, matching issues, and uncertainty with outcomes. Additionally, subsequent large prospective trials with rifaximin in patients with advanced liver disease failed to show a signal related to infections or DROs.[29,30]

Our data extends these prior analyses into a prospective global representative cohort which we isolated to only those who had infections. This reduces the risk of skewing by excluding non-infected individuals, in whom DROs would not be clinically sought. In our infected patient cohort, rifaximin was used in 30% of patients mostly for HE and majority of them started this within 6 months of the admission. As expected, rifaximin users were more advanced in their disease process compared to those who were not on it.[22] And on crude comparisons, HE, lactulose and rifaximin were associated with DRO emergence. However, when controlled for all clinical variables, and country income levels, we did not find a significant association between rifaximin use on admission and isolation of DROs. This was consistent across country income levels. The results remained consistent even after multiple sensitivity analyses, such as inclusion of mortality, after propensity-score matching, and after analyzing HE diagnoses and HE therapies. Therefore, it is likely that the association of rifaxi-

min with DROs is clinically a reflection of the patients in whom rifaximin is started rather than the rifaximin itself. Rifaximin has grade A evidence to reduce HE recurrence and a potentially small risk of increase in resistance that does not necessarily translate into infections or is clinically significant, and needs to be balanced against the higher risk of HE recurrence.[31-33] HE recurrence remains the most important preventable readmission among patients with cirrhosis, and the risk-benefit ratio of withholding rifaximin therapy should be carefully thought out.[34-37]

To further investigate the findings of Turner et al.[8], we focused on daptomycin and the potential for VRE, both of which are relatively rare in cirrhosis. In our current cohort 1.5% of patients were on daptomycin. Rifaximin use was equally distributed in patients with/without daptomycin use, and there was no statistically significant difference of VRE distribution with rifaximin. Daptomycin use was linked with higher DRO emergence and poor outcomes as expected, being a last-resort antibiotic. There was no consistent impact, and these daptomycin results mirroring previously published data in cirrhosis are likely not clinically significant.[11]

The DRO isolation rate depends on the awareness and availability of performing prompt cultures, which can vary worldwide.[7] Approximately half of our infections were culture-positive, and a quarter had DROs. However, despite the limitations we found a similar rate of DROs across country income levels in this cohort. In addition, rifaximin use was higher in L/LMICs, which argues against potential lack of access to medications in these countries. Ultimately, we found no significant impact of rifaximin on DRO emergence regardless of country income levels. While higher MELD-Na is expected to be associated with more advanced liver disease and DROs, we found that male sex and HBV etiology were protective. The reasons behind these are unclear but these were driven by UMICs, especially China and Türkiye since they were also significant when isolated to these countries. The gender differences in sites of infection could explain this phenomenon partly as well. Since we restricted our cohort to only patients with infections, we did not find a major impact of SBP prophylaxis or PPIs on DROs. The specific impact of prior HE and AKI/HRS and associated medications on DROs is interesting since these have emerged as the major causes of admission in cirrhosis.[38] Therefore, these are likely markers of hospital exposure rather than inherent risk factors.[15]

The representative nature of the data with a maximum of 100 subjects per site prevents skewing of the data from centers with higher resistance and is a strength. The granular nature of the data, uniform definitions, and central data capture with quality control across the CLEARED database is another strength. The limited number of patients per site (N=100) could reduce the generalizability with varying resources for infection management. Additionally, these were a risk of death occurring prior to DRO development, which could be addressed through the usage of competing risks regression. However, time-to-event data was not available in this cohort, which is a limitation.

In summary, in a prospectively enrolled inpatient cohort of infected patients with cirrhosis, DROs were isolated in 12% of infections, which did not vary significantly between country income levels. While prior HE and AKI, and lactulose and rifaximin use were significantly higher on crude analysis for DRO emergence, these were not significant on multivariable analysis. We conclude that rifaximin use was not associated with DRO emergence in this global cohort of inpatients with cirrhosis.

Authors' contribution

JSB conceptualized the study question, SS was involved in statistical analysis, BJB was responsible for data quality and curation, AC, PSK, FW, QX, RI, MT, WKS, AT, PH, JG, and MAS are part of the Steering committee for CLEARED who were involved in critical revisions and study conduct. All other investigators were involved in study conduct.

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AI was used to create the graphical abstract using Notebook LLM. There are no other uses of AI in the manuscript.

Conflicts of Interest

JSB's institution receives grant support from Bausch. None for any other collaborator.

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SUPPLEMENTARY MATERIAL

Supplementary material is available at Clinical and Molecular Hepatology website (http://www.e-cmh.org).

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