Received: 13 February 2017 | First decision: 26 March 2017 | Accepted: 30 July 2017

DOI: 10.1111/apt.14275

WILEY AP&T Alimentary Pharmacology & Therapeutics

# Rifaximin treatment is associated with reduced risk of cirrhotic complications and prolonged overall survival in patients experiencing hepatic encephalopathy

S. H. Kang[1,2,*] | Y. B. Lee[3,*] | J.-H. Lee[1] | J. Y. Nam[1] | Y. Chang[1] | H. Cho[1] | J.-J. Yoo[1] | Y. Y. Cho[1] | E. J. Cho[1] | S. J. Yu[1] | M. Y. Kim[2] | Y. J. Kim[1] | S. K. Baik[2] | J.-H. Yoon[1]

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea

[2]Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea

[3]Department of Internal Medicine, CHA Bundang Medical Center, CHA University, Seongnam, Korea

**Correspondence**
Prof. J-H Lee, Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea.
Emails: pindra@empal.com or JHLeeMD@gmail.com

**Funding information**
This study was funded by grants from the Seoul National University Hospital (grant number: 3020160190 [2016-1388]) and Supporting Program of the Korean Association for the Study of the Liver.

## Summary

**Background:** Rifaximin might decrease the risk of portal hypertension-related complications by controlling small intestinal bacterial overgrowth.

**Aim:** To evaluate whether rifaximin was associated with the risk of death and cirrhotic complications.

**Methods:** We conducted a retrospective study that included 1042 patients experiencing hepatic encephalopathy (HE): 421 patients without hepatocellular carcinoma (HCC; the non-HCC cohort) and 621 patients with HCC (the HCC cohort). The primary endpoint was overall survival and secondary endpoints were recurrence of HE and the development of spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS) and variceal bleeding.

**Results:** In the non-HCC cohort, 145 patients received rifaximin plus lactulose (the rifaximin group) and 276 patients received lactulose alone (the control group). The multivariate analysis revealed that rifaximin was significantly associated with lower risk of death (adjusted hazard ratio [aHR], 0.697; $P = .024$) and reduced the risk of recurrent HE (aHR, 0.452; $P < .001$), SBP (aHR, 0.210; $P < .001$) and variceal bleeding (aHR, 0.425; $P = .011$) but not HRS (aHR, 0.598; $P = .08$). In the HCC cohort, 173 patients received rifaximin plus lactulose and 448 patients received lactulose. Rifaximin was not associated with the risk of death (aHR, 1.177; $P = .121$). Rifaximin was associated with lower risk of SBP (aHR, 0.323; $P < .001$) but not with variceal bleeding (aHR, 0.660; $P = .104$) or recurrent HE (aHR, 0.689; $P = .057$). The risk of *Clostridium difficile*-associated diarrhoea was not different between the groups (aHR, 0.028; $P = .338$).

**Conclusions:** In patients without HCC, rifaximin treatment was significantly associated with prolonged overall survival and reduced risks of spontaneous bacterial peritonitis, variceal bleeding and recurrent hepatic encephalopathy.

*These two authors contributed equally to this work.

The Handling Editor for this article was Professor Grace Wong, and it was accepted for publication after full peer-review.

  

## 1 | INTRODUCTION

Cirrhosis is one of the leading causes of death worldwide, and it is associated with a significant reduction in health-related quality of life and it places a considerable burden on health care systems.[1] According to data from the World Health Organization, cirrhosis is the 12th leading cause of death worldwide, accounting for more than 1 million deaths in 2012.[2] The cost associated with treatment for cirrhosis in 2008 ranged from $14 million to $2 billion, depending on disease aetiology.[3] Portal hypertension may contribute to the development of cirrhotic complications, including ascites, hepatic encephalopathy (HE), spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS) and variceal bleeding.[4] The ultimate cure for end-stage cirrhosis is liver transplantation.[5] However, in many parts of the world, transplants are not readily available, and, in countries where transplants are available, demand for organs far exceeds supply and high costs associated with transplantation are prohibitive. Moreover, few medical treatments have been discovered that can prolong overall survival in patients with decompensated cirrhosis, except for aetiology-specific treatment (eg, oral anti-viral treatment for hepatitis B virus-related cirrhosis)[6] or case-specific treatment (eg, nonselective beta-blockers [NSBB] or endoscopic variceal ligation [EVL] for patients with variceal bleeding).[7,8]

Recently, several studies reported that progressive gut microbiota changes occur in patients with cirrhosis, and these changes may be involved in the pathogenesis of cirrhotic complications.[9,10] The prevalence of small bowel bacterial overgrowth in patients with cirrhosis is high, ranging between 30% and 70%.[11] The bacterial overgrowth may increase intestinal permeability and translocation, as well as increase levels of endotoxin and circulating pro-inflammatory cytokines, which may contribute to the pathogenesis of portal hypertension-related cirrhotic complications.[12,13] In this context, oral antibiotics might help to reduce the small intestinal bacterial overgrowth, possibly preventing cirrhotic complications. A prospective study reported that selective intestinal decontamination with a fluoroquinolone, norfloxacin, is effective for preventing a recurrence of SBP.[14] However, there is concern that widespread prophylaxis with norfloxacin might lead to the development of antibiotic-resistant bacteria since norfloxacin is a systemic antibiotic.

Rifaximin, a semisynthetic derivative of rifamycin, is minimally absorbed into systemic circulation and has broad-spectrum in vitro activity against both aerobic and anaerobic enteric bacteria. It has a low risk of inducing systemic bacterial resistance.[15,16] Therefore, we postulated that rifaximin might decrease the risk of portal hypertension-related complications in patients with cirrhosis regardless of underlying aetiology, which might increase survival in patients with advanced cirrhosis. In fact, a recent randomised, double-blind clinical trial showed that rifaximin maintained remission from HE and reduced the risk of HE-related hospitalisation.[17] Moreover, a recent open-label maintenance study confirmed the safety and efficacy of rifaximin for reducing the risk of HE recurrence.[18] However, the overall effect of rifaximin in patients with cirrhosis has not been fully evaluated in a large-scale cohort.

In this study, we aimed to evaluate whether rifaximin could prolong overall survival and reduce the risks of various cirrhotic complications, other than hepatic encephalopathy (HE), in patients with decompensated cirrhosis.

## 2 | MATERIAL AND METHODS

### 2.1 | Patients

We conducted a retrospective cohort study. Initially, we enrolled 1467 consecutive patients who were diagnosed with cirrhosis-associated HE and recovered after medical treatment at a single tertiary hospital (Seoul National University Hospital, Seoul, Korea) from January 2010 to June 2015 (Figure 1). The remaining 1042 patients constituted our study population. Exclusion criteria are listed in Data S1. Since the impact of treatment regimens on overall survival differed according to the presence of hepatocellular carcinoma (HCC) (Figure S1), which was confirmed by the interaction plots indicating significant interaction between the presence of HCC and treatment effect of rifaximin (Figure S2), we stratified the entire cohort into the non-HCC and HCC groups and analysed the effect of rifaximin treatment in each cohort. Two cohorts were established according to the presence of HCC at the time of developing HE: the HCC and non-HCC cohorts. Patients were also divided into groups according to treatment regimens for HE: the rifaximin group (patients treated with rifaximin plus lactulose) and the control group (patients treated with lactulose without rifaximin). Management strategies for HE, including rifaximin, were chosen by each clinician's decision. Then, the rifaximin group comprised all patients, with or without HCC, who were treated with rifaximin (600 mg twice a day) and lactulose (30-60 mL 3 times a day); the control group comprised all patients treated with lactulose only. The physicians instructed patients to achieve the titration target with lactulose so that patients had 2-3 semiformed stools/day for prevention of recurrent HE. The dose of lactulose was assessed during every clinic visit.

Cirrhosis was diagnosed on the basis of clinical findings: (i) platelet count of less than 100 000/μL and ultrasonography findings suggestive of cirrhosis, including a blunted, nodular liver edge accompanied by splenomegaly (bipolar diameter >12 cm) or (ii) clinical signs of portal hypertension, such as ascites, oesophageal or gastric varices, and HE.[19] The presence of ascites was confirmed with abdominal ultrasound or computed tomography (CT) and varices were evaluated by oesophagogastroduodenoscopy or abdominal dynamic CT.

HE was diagnosed on the basis of neuromuscular signs and the West Haven scale (HE; grade ≥2, remission of HE; grade 0 or 1) which is based on alterations in the state of consciousness, intellectual function and behavior. Reports of HE including confusion and memory loss in patients were obtained from clinical notes.

### 2.2 | Clinical outcomes and follow-up evaluation

The primary endpoint of our study was overall survival. Secondary endpoints included recurrence of HE and the development of SBP, HRS and variceal bleeding. Definitions of clinical outcomes are

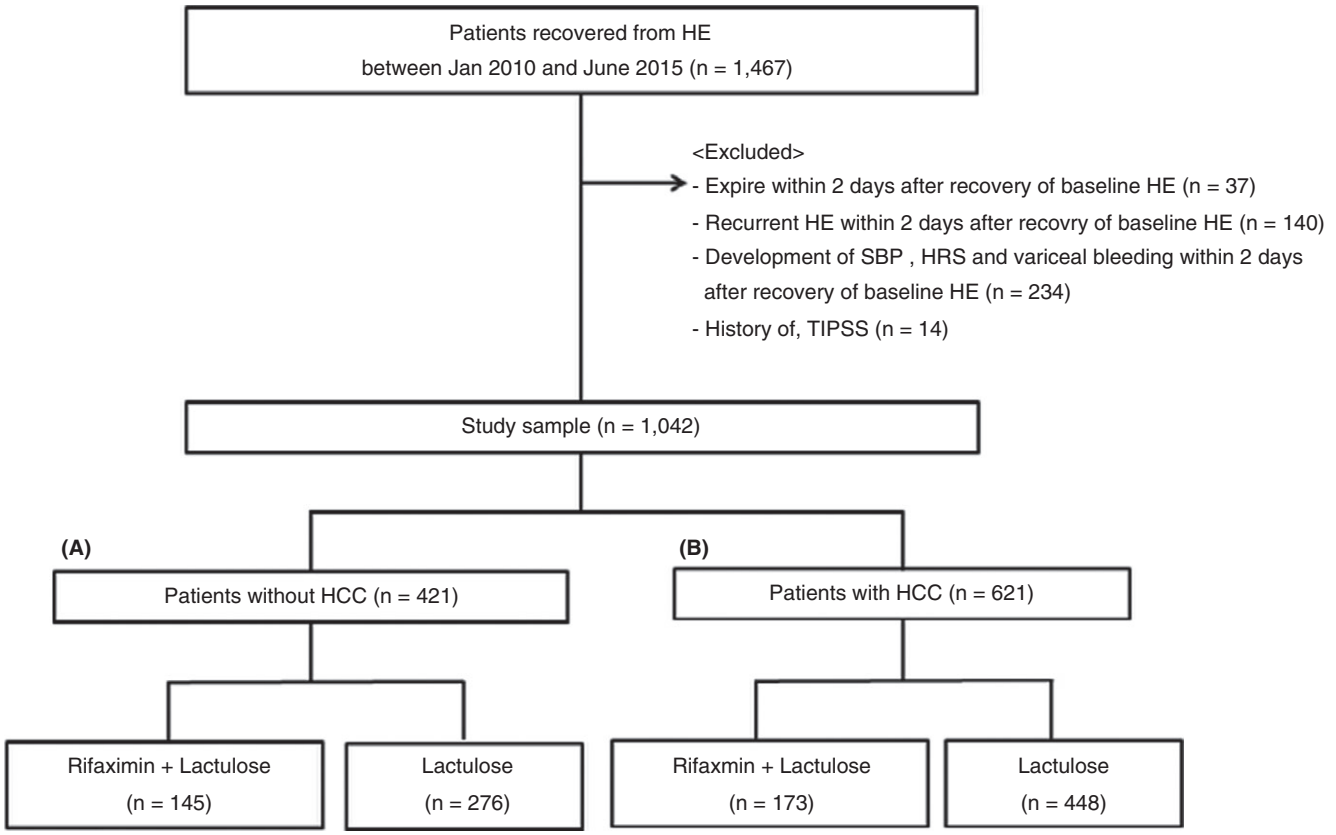


**FIGURE 1** Patient flow diagram. Patients were excluded from the study if they experienced a primary or secondary endpoint, including SBP, HRS, or variceal bleeding, within 2 days after recovery of baseline HE or had a history of transjugular intrahepatic portosystemic shunt. A, Patients without HCC who received rifaximin and lactulose treatment (n = 145) and lactulose-only treatment (n = 276). B, Patients with HCC who received rifaximin and lactulose treatment (n = 173) and lactulose-only treatment (n = 448). HE, hepatic encephalopathyh; SBP, spontaneous bacterial peritonitis; HRS, hepatorenal syndrome; TIPSS, transjugular intrahepatic porto-systemic shunt; HCC, hepatocellular carcinoma

provided in Data S1. The index date of follow-up is the date of discharge after full recovery from baseline HE. All outcomes were evaluated at the maximum duration of follow-up. The date of all-cause mortality was obtained from patients' medical records and from the Korean Ministry of Government Administration and Home Affairs. The date of an event was defined as the first event date from the index date. Medication possession rate was calculated by the total days of medication supply divided by time interval. We used a Medication possession rate cutoff value for adherence of >80%.[20]

We evaluated clinical variables such as age, sex, past medical history, and results of laboratory tests at baseline before treatment. We calculated the Child–Turcotte–Pugh scores and TNM stage using standard clinical, laboratory and image findings. We performed TNM staging according to the American Joint Committee on Cancer Staging Manual (7th edition). This study was approved by the Institutional Review Board of Seoul National University Hospital (H-1605-021-760), and the requirement for informed consent was waived. This study was performed in accordance with the Declaration of Helsinki.

## 2.3 | Statistical analyses

We analysed the non-HCC and HCC cohorts separately and used the chi-square test and the independent *t*-test to evaluate the differences in clinical variables between the rifaximin group and the lactulose group. We used Cox proportional hazards models to assess the influence of the clinical variables on endpoints. For the multivariate analysis, we included covariates with $P < .05$ in the univariate analysis.

We calculated the cumulative rates of overall survival, HE recurrence, SBP development, HRS and variceal bleeding using the Kaplan–Meier method and censoring the patients who were lost to follow-up. We performed the log-rank test to compare the differences between the groups.

We used inverse probability weighting based on the propensity score to adjust for differences in baseline characteristics.[21,22] We calculated a propensity score for each patient using a logistic regression model that included the baseline characteristics. The 2 groups were balanced using an inverse probability weight for each patient, which was generated on the basis of the propensity score (Table S1). After performing inverse probability weighting, we assessed the balance of baseline characteristics between the groups, and then we fit weighted Cox proportional hazards models.

For statistically significant primary outcomes, the number needed to treat (NNT) was calculated using 1/risk difference. A $P < 0.05$ was considered statistically significant. The statistical analyses were

performed using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA) and R language, version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

## 3 | RESULTS

### 3.1 | Baseline characteristics

This study involved 421 patients without HCC (the non-HCC cohort) and 621 patients with HCC (the HCC cohort). Among 421 patients of the non-HCC cohort, 145 patients received a combination of rifaximin and lactulose (the rifaximin group) and 276 received lactulose alone (the control group). These 2 groups did not differ in mean age, sex distribution or aetiology of liver cirrhosis (Table 1A). At baseline, the proportion of patients experiencing previous HE was higher in the rifaximin group than in the control group (31.7% vs 22.1%, $P = 0.04$). The Child–Turcotte–Pugh score was not significantly different between the groups.

In the HCC cohort (n = 621), 173 patients received a combination of rifaximin and lactulose (the rifaximin group) and 448 received lactulose alone (the control group). Baseline characteristics were similar in the 2 groups, except that the proportion of patients with a previous episode of HE was higher in the control group (Table 1B). The Child–Turcotte–Pugh score and TNM stage were not significantly different between the groups.

Median follow-up durations were 18.0 months (interquartile range, 4.3-36.3 months) in the non-HCC cohort and 4.4 months (interquartile range, 1.3-16.4 months) in the HCC cohort.

The proportions of patients with varices at baseline, and who received prophylactic treatment (ie, EVL or NSBB) did not differ significantly between the groups in both non-HCC and HCC cohorts. The prevalence of portal vein thrombosis (PVT) was also comparable between the groups among both non-HCC and HCC cohorts. Most patients with chronic hepatitis B were treated with an anti-viral agent according to the international practice guidelines.[23,24] Medication possession rate of the rifaximin exceeded 80%, which indicates good adherence to drug, in both the HCC and non-HCC cohorts.

### 3.2 | Overall survival

In the non-HCC cohort, 210 (49.8%) patients died during the follow-up period: 53 in the rifaximin group and 157 in the control group. The cumulative probabilities of survival at 12, 24, 36 and 48 months were 70.3%, 67.6%, 64.1% and 63.4% in the rifaximin group and 63.0%, 54.3%, 47.8% and 44.9% in the control group respectively (Figure 2A). Univariate analysis showed that rifaximin treatment (hazard ratio [HR], 0.690; 95% confidence interval [CI], 0.505-0.944; $P = .02$) and Child–Turcotte–Pugh class A/B (vs Child–Turcotte–Pugh class C) was significantly associated with lower risk of death (HR, 0.560; 95% CI, 0.422-0.741; $P < .001$). Multivariate analysis showed that rifaximin treatment was associated with lower risk of death (adjusted HR [aHR], 0.697; 95% CI, 0.510-0.954; $P = .024$) after adjusting for Child–Turcotte–Pugh class (Tables 2A and S2A).

A cost-effectiveness analysis showed that 9.6 patients would need to be treated with rifaximin to increase the survival rate of 1 patient each year (ie, NNT = 9.6). The cost of rifaximin for 1 year was $7440. For patients without HCC, the 1-year incremental cost to increase survival in 1 patient experiencing HE was $71 424.

In the HCC cohort, 501 (80.6%) patients died during the follow-up period: 130 in the rifaximin group and 371 in the control group. The cumulative probabilities of overall survival at 12, 24, 36 and 48 months were 38.2%, 27.7%, 26.0% and 24.9% in the rifaximin group and 35.9%, 25.0%, 19.6% and 18.1% in the control group respectively (Figure 2B). Univariate analysis showed that high alanine aminotransferase (ALT) levels (≥40 IU/L), previous history of HE, Child–Turcotte–Pugh class C and TNM stage were significantly associated with risk of death; rifaximin treatment was not associated with the risk of death. Multivariate analysis showed that rifaximin was not related to lower risk of death (aHR, 1.177; 95% CI, 0.958-1.447; $P = .121$) after adjusting for Child–Turcotte–Pugh class and TNM stage (Tables 2B and S2B).

In the entire cohort (n = 1042), rifaximin treatment was significantly associated with lower risk of death even after adjusting for the interaction term before and after inverse probability weighting ($P = .047$ and .036 respectively) (Table S3).

### 3.3 | Complications of portal hypertension

In the non-HCC cohort, 115 patients experienced HE recurrence after recovery of baseline HE: 23 in the rifaximin group and 92 in the control group. The rifaximin group showed a significantly lower risk of recurrent HE than the control group (HR, 0.449; 95% CI, 0.284-0.711; $P < .001$) (Figure 3, left upper panel). In the multivariate analysis, rifaximin treatment was an independent negative risk factor for HE recurrence (aHR, 0.452; 95% CI, 0.286-0.715; $P < .001$) (Table 2A). These data suggest that 6.1 patients would need to be treated with rifaximin to prevent an episode of recurrent HE for 1 year (ie, NNT = 6.1).

During the follow-up period, 128 patients without HCC developed SBP: 10 (6.8%) in the rifaximin group and 118 (42.7%) in the control group. Patients who received rifaximin had a significantly lower probability of developing SBP (HR, 0.213; 95% CI, 0.111-0.408; $P < .001$) than patients who received lactulose alone (Figure 3, right upper panel). Multivariate Cox regression analysis showed that rifaximin was significantly associated with lower risk of developing SBP (aHR, 0.210; 95% CI, 0.110-0.402; $P < .001$) after adjusting for the presence of diabetes mellitus and Child–Turcotte–Pugh class (Table 2A). These data suggest that 5.4 patients would need to be treated with rifaximin to prevent SBP for 1 year (ie, NNT = 5.4).

A total of 64 patients without HCC experienced variceal bleeding: 11 (7.5%) in the rifaximin group and 53 (19.2%) in the control group. During the follow-up period, patients who received rifaximin had a significantly lower probability of variceal bleeding than patients in the control group (HR, 0.402; 95% CI, 0.210-0.770; $P = .006$) (Figure 3, left lower panel). In the multivariate analysis, rifaximin treatment (aHR, 0.425; 95% CI, 0.220-0.821; $P = .011$) was an independent

**TABLE 1** Baseline characteristics of patients with and without hepatocellular carcinoma (HCC) according to treatment group

| (A) Patients in the non-HCC cohort | Rifaximin + lactulose N = 145 | Lactulose N = 276 | *P*-value |
|---|---|---|---|
| Age (y)[a] | 58.60 ± 11.49 | 60.22 ± 12.04 | .163 |
| Male | 92 (63.4) | 167 (60.5) | .628 |
| Aetiology of cirrhosis | | | |
| Viral | 64 (44.1) | 126 (45.6) | .471 |
| Alcohol | 55 (37.9) | 90 (32.6) | |
| Others | 26 (17.9) | 60 (21.7) | |
| Previous HE | 46 (31.7) | 61 (22.1) | .041 |
| Child–Turcotte–Pugh score[b] | 10.0 [8.0, 11.0] | 10.0 [8.2, 11.0] | .089 |
| Child–Turcotte–Pugh class | | | |
| A | 7 (4.8) | 8 (2.9) | .429 |
| B | 63 (43.4) | 111 (40.2) | |
| C | 75 (51.7) | 157 (56.8) | |
| HTN | 35 (24.1) | 66 (23.9) | 1.000 |
| DM | 46 (31.7) | 90 (32.6) | .940 |
| ALT, IU/L | | | |
| <40 | 101 (69.7) | 183 (66.3) | .557 |
| ≥40 | 40 (30.3) | 93 (33.7) | |
| Albumin, g/dL | | | |
| <3.3 | 54 (37.2) | 84 (30.4) | .157 |
| ≥3.3 | 91 (62.8) | 192 (69.6) | |
| Total bilirubin, mg/dL | | | |
| <1.6 | 38 (26.2) | 56 (20.3) | .166 |
| ≥1.6 | 107 (73.8) | 220 (79.7) | |
| PT, INR | | | |
| <1.3 | 47 (32.4) | 84 (30.4) | .677 |
| ≥1.3 | 98 (67.6) | 192 (69.6) | |
| Presence of varices | 81 (55.9) | 150 (54.3) | .589 |
| Prophylactic treatment for varices (EVL or NSBB) | 68 (46.9) | 113 (40.9) | .241 |
| Presence of portal vein thrombosis | 11 (7.6) | 13 (4.7) | .275 |

(Continues)

negative risk factors of variceal bleeding in the non-HCC cohort after adjustment for the presence of varices, prophylactic treatment (EVL or NSBB) and baseline ALT level (Table 2A). These data suggest that 11.0 patients would need to be treated with rifaximin to prevent an episode of variceal bleeding for 1 year (ie, NNT = 11.0).

A total of 71 patients without HCC developed HRS: 15 (10.3%) in the rifaximin group and 56 (20.3%) in the control group. Although not statistically significant, the risk of developing of HRS was slightly lower in the rifaximin group than in the control group (HR, 0.594; $P = .077$) (Figure 3, right lower panel).

**TABLE 1** (Continued)

| (B) Patients in the HCC cohort | Rifaximin + lactulose N = 173 | Lactulose N = 448 | *P*-value |
|---|---|---|---|
| Age, y[a] | 63.28 ± 9.8 | 64.23 ± 9.9 | .332 |
| Male | 143 (82.6) | 351 (78.3) | .278 |
| Aetiology of cirrhosis | | | |
| Viral | 134 (77.4) | 353 (78.7) | .926 |
| Alcohol | 24 (13.9) | 59 (13.2) | |
| Others | 15 (8.7) | 36 (8.0) | |
| Previous HE | 52 (30.0) | 61 (13.6) | <.001 |
| Child–Turcotte–Pugh score[b] | 9.0 [8.0, 11.0] | 10.0 [8.0, 11.0] | .053 |
| Child–Turcotte–Pugh class | | | |
| A | 4 (2.3) | 10 (2.2) | .361 |
| B | 83 (47.9) | 187 (41.7) | |
| C | 86 (49.7) | 251 (56.0) | |
| HTN | 43 (24.8) | 143 (31.9) | .104 |
| DM | 59 (34.1) | 168 (37.5) | .487 |
| TNM stage | | | |
| I | 39 (22.5) | 71 (15.9) | .120 |
| II | 45 (26.0) | 128 (28.6) | |
| III | 44 (25.4) | 145 (32.4) | |
| IV | 45 (26.0) | 104 (23.2) | |
| ALT, IU/L | | | |
| <40 | 84 (48.6) | 183 (40.9) | .099 |
| ≥40 | 89 (51.4) | 265 (59.1) | |
| Albumin, g/dL | | | |
| <3.3 | 51 (29.5) | 125 (27.9) | .696 |
| ≥3.3 | 122 (70.5) | 323 (72.1) | |
| Total bilirubin, mg/dL | | | |
| <1.6 | 46 (26.6) | 106 (23.7) | .447 |
| ≥1.6 | 127 (73.4) | 342 (76.3) | |
| PT, INR | | | |
| <1.3 | 48 (27.7) | 111 (24.8) | .447 |
| ≥1.3 | 125 (72.3) | 337 (75.2) | |
| Presence of varices | 81 (46.8) | 199 (44.4) | .909 |
| Prophylactic treatment for varices (EVL or NSBB) | 55 (31.8) | 133 (29.7) | .609 |
| Presence of portal vein thrombosis | 27 (15.6) | 66 (14.7) | .784 |

Data are given as number (%) of patients unless otherwise indicated.
ALT, alanine aminotransferase; EVL, endoscopic variceal ligation; HE, hepatic encephalopathy; INR, international normalised ratio; PT, prothrombin time; NSBB, non-selective beta-blockers.
[a]Data are reported as mean (±standard deviation).
[b]Data are reported as median [25th, 75th percentiles].

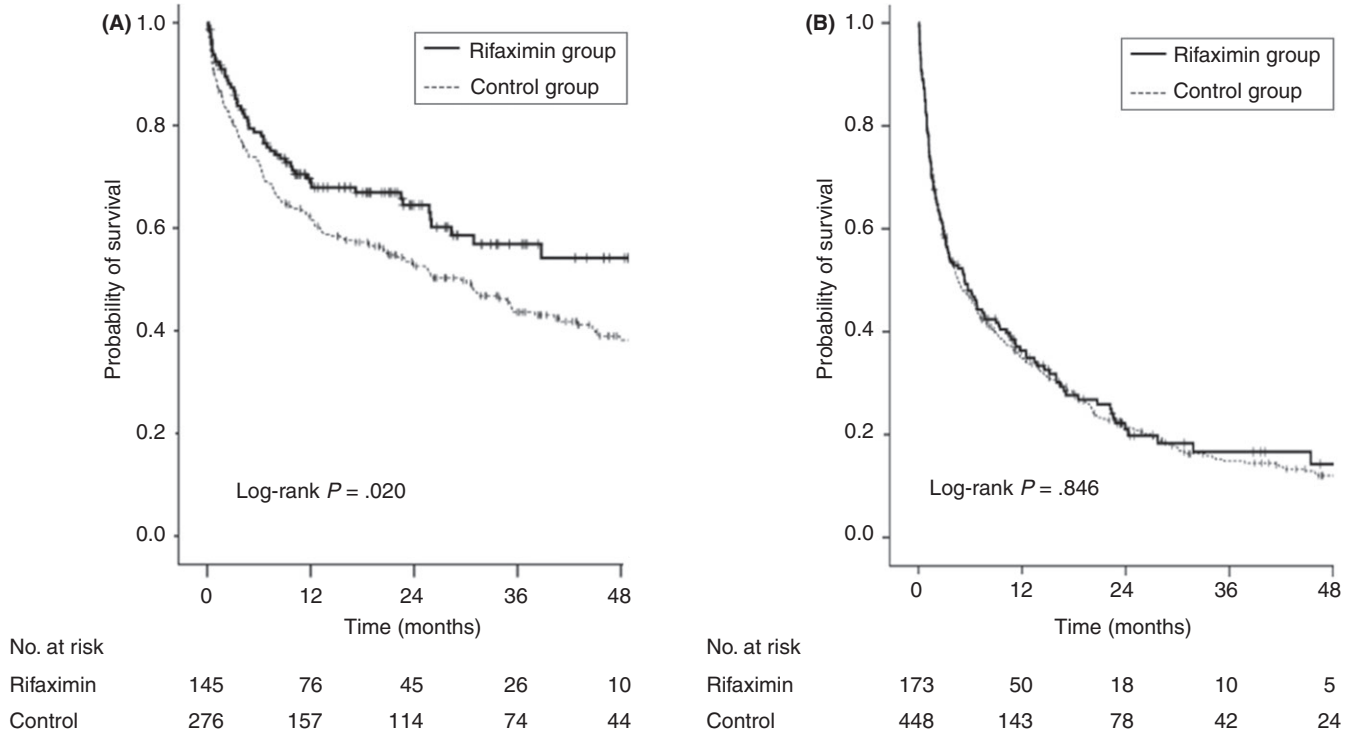


**FIGURE 2** Kaplan–Meier estimates of overall survival according to treatment group. The solid lines represent overall survival in the rifaximin group and the dotted lines represent overall survival in the control group. A, In the non-HCC cohort, the rifaximin group showed significantly higher overall survival than the control group. B, In the HCC cohort, the rifaximin group showed similar overall survival to the control group

In the HCC cohort, 164 patients experienced HE recurrence after recovery of baseline HE: 33 (19.0%) in the rifaximin group and 131 (29.2%) in the control group. The HR for the risk of recurrent HE in the rifaximin group compared with the control group was 0.656 (95% CI, 0.448-0.961; $P = .030$) (Figure 4, left upper panel). In the multivariate analysis, rifaximin treatment tended to reduce the risk of recurrent HE (aHR, 0.689; 95% CI, 0.469-1.013; $P = .057$) (Table 2B). These data suggest that 9.3 patients would need to be treated with rifaximin to prevent an episode of recurrent HE for 1 year (ie, NNT = 9.3).

During the follow-up period, 227 patients with HCC developed SBP: 22 (12.7%) in the rifaximin group and 205 (48.7%) in the control group. Patients who received rifaximin had a significantly lower probability of developing SBP than the control group (HR, 0.323; 95% CI, 0.208-0.502; $P < .001$) (Figure 4, right upper panel). Multivariate Cox regression analysis of relevant variables showed that rifaximin was associated with lower risk of developing of SBP (aHR, 0.383; 95% CI, 0.245-0.600; $P < .001$) after adjusting for Child–Turcotte–Pugh class and TNM stage (Table 2B). These data suggest that 3.7 patients would need to be treated with rifaximin to prevent SBP for 1 year (ie, NNT = 3.7).

A total of 105 patients with HCC developed variceal bleeding: 19 (10.9%) patients in the rifaximin group and 86 (19.1%) in the control group. During the follow-up period, patients who received rifaximin had a significantly lower probability of variceal bleeding than the control group (HR, 0.604; 95% CI, 0.367-0.993; $P = .047$) (Figure 4, left lower panel). According to the multivariate analysis, rifaximin treatment was not an independent predictor of variceal bleeding (aHR, 0.660; $P = .104$) after adjusting for the presence of varices, prophylactic treatment (EVL or NSBB), presence of PVT, sex and TNM stage of HCC (Table 2B). The rifaximin group showed a trend towards a lower risk of developing of HRS than the control group in the HCC cohort, but the difference was not statistically significant (HR, 0.812; $P = .292$) (Figure 4, right lower panel).

In the entire cohort, the associations between rifaximin treatment and clinical outcomes, including recurrence of HE ($P < .001$), SBP ($P < .001$) and variceal bleeding ($P = .001$), were significant (Table S4A).

## 3.4 | Inverse probability weighting analysis

In the non-HCC cohort, the baseline characteristics, including the proportion of patients with a previous episode of HE, became more balanced between the groups after adjustment using inverse probability weighting (Table S1A). In the multivariate weighted Cox regression analysis, rifaximin was significantly associated with lower risk of death (aHR, 0.718; 95% CI, 0.520-0.992; $P = .044$) and reduced of recurrent HE (aHR, 0.461; 95% CI, 0.288-0.740; $P = .001$), SBP (aHR, 0.222; 95% CI, 0.114-0.435; $P < .001$), and variceal bleeding (aHR, 0.387; 95% CI, 0.197-0.758; $P = .006$) but not HRS (aHR, 0.568; $P = .057$) (Table S5A).

**TABLE 2** Variables independently associated with endpoints in patients with and without hepatocellular carcinima (HCC)

| (A) Patients in the non-HCC cohort | | | |
|---|---|---|---|
| | Multivariate Cox regression analysis | | |
| Variable | Subgroup | HR (95% CI) | *P*-value |
| Overall survival | | | |
| Rifaximin | yes vs no | 0.697 (0.510–0.954) | .024 |
| Child–Turcotte–Pugh class | A/B vs C | 0.562 (0.424–0.745) | <.001 |
| Recurrence of HE | | | |
| Rifaximin | yes vs no | 0.452 (0.286–0.715) | <.001 |
| DM | yes vs no | 1.477 (1.017–2.145) | .041 |
| Spontaneous bacterial peritonitis | | | |
| Rifaximin | yes vs no | 0.210 (0.110–0.402) | <.001 |
| DM | yes vs no | 1.530 (1.076–2.175) | .018 |
| Child–Turcotte–Pugh class | A/B vs C | 0.475 (0.313–0.656) | <.001 |
| Variceal bleeding | | | |
| Rifaximin | yes vs no | 0.425 (0.220–0.821) | .011 |
| Presence of varices | yes vs no | 3.203 (1.728–5.935) | <.001 |
| Prophylactic treatment (EVL or NSBB) | yes vs no | 0.537 (0.303–0.955) | .034 |
| Presence of PVT | yes vs no | 1.528 (0.542–4.306) | .423 |
| Serum ALT level (IU/L) | <40 vs ≥40 | 0.361 (0.178–0.734) | .005 |
| Hepatorenal syndrome | | | |
| Rifaximin | yes vs no | 0.595 (0.334–1.060) | .078 |
| Serum ALT level (IU/L) | <40 vs ≥40 | 0.544 (0.307–0.964) | .037 |

(Continues)

**TABLE 2** (Continued)

| (B) Patients in the HCC cohort | | | |
|---|---|---|---|
| | Multivariate Cox regression analysis | | |
| Variable | Subgroup | HR (95% CI) | *P*-value |
| Overall survival | | | |
| Rifaximin | yes vs no | 1.177 (0.958–1.447) | .121 |
| Child–Turcotte–Pugh class | A/B vs C | 0.478 (0.399–0.573) | <.001 |
| TNM stage | I vs II | 0.556 (0.405–0.764) | <.001 |
| | I vs III | 0.251 (0.184–0.343) | <.001 |
| | I vs IV | 0.140 (0.101–0.194) | <.001 |
| Recurrence of HE | | | |
| Rifaximin | yes vs no | 0.689 (0.469–1.013) | .057 |
| TNM stage | I vs IV | 0.490 (0.294–0.816) | .006 |
| Spontaneous bacterial peritonitis | | | |
| Rifaximin | yes vs no | 0.383 (0.245–0.600) | <.001 |
| Child–Turcotte–Pugh class | A/B vs C | 0.426 (0.324–0.561) | <.001 |
| TNM stage | I vs III | 0.517 (0.349–0.765) | <.001 |
| | I vs IV | 0.394 (0.256–0.606) | <.001 |
| Variceal bleeding | | | |
| Rifaximin | yes vs no | 0.660 (0.400–1.089) | .104 |
| Presence of varices | yes vs no | 1.078 (0.593–1.959) | .806 |
| Prophylactic treatment (EVL or NSBB) | yes vs no | 1.005 (0.529–1.911) | .988 |
| Presence of PVT | yes vs no | 0.775 (0.366–1.644) | .507 |
| Sex | Female vs male | 0.529 (0.304–0.921) | .024 |
| TNM stage | I vs IV | 3.251 (1.708–6.190) | <.001 |
| Hepatorenal syndrome | | | |
| Rifaximin | yes vs no | 0.992 (0.666–1.476) | .968 |
| Child–Turcotte–Pugh class | A/B vs C | 0.486 (0.350–0.675) | <.001 |
| TNM stage | I vs II | 0.509 (0.302–0.858) | .011 |
| | I vs III | 0.340 (0.199–0.583) | <.001 |
| | I vs IV | 0.235 (0.131–0.421) | <.001 |

ALT, alanine aminotransferase; EVL, endoscopic variceal ligation; HE, hepatic encephalopathy; HR, hazard ratio; NSBB, non-selective beta-blockers; PVT, portal vein thrombosis.

In the HCC cohort, the baseline characteristics became more balanced between the groups after adjustment using inverse probability weighting (Table S1B). In the multivariate weighted Cox regression analysis, rifaximin was not related to lower risk of death (aHR, 1.213; $P = .073$) (Table S5B). Rifaximin was not significantly associated with a reduced risk of variceal bleeding (aHR, 0.701; $P = .200$) or HRS (aHR, 0.983; $P = .934$). However, rifaximin treatment was significantly associated with lower risk of developing recurrent HE (aHR, 0.653; 95% CI, 0.434-0.982; $P = .041$) and SBP (aHR, 0.337; 95% CI, 0.208-0.546; $P < .001$) in patients with HCC (Table S5B).

In the entire cohort, the associations of rifaximin treatment with clinical outcomes, including overall survival ($P = .036$), HE ($P < .001$), SBP ($P < .001$), and variceal bleeding ($P = .028$), were confirmed after inverse probability weighting (Tables S3B and S4B).

## 3.5 | Adverse events

Eight patients developed the *C. difficile*-associated diarrhoea during follow-up period: 1 patient in the rifaximin group and 7 in the control group. The risk of *C. difficile*-associated diarrhoea was not significantly different between the groups ($P = .338$).

Of the 355 patients with development of SBP, positive ascites cultures were detected in 39 (11.0%) patients: 11 in the rifaximin group and 28 in the control group (Table S6). All cases of SBP in the rifaximin group were associated with infection with Gram-negative bacteria. In the control group, Gram-negative bacteria were isolated from 25 cases and Gram-positive bacterial infections were reported in 3 cases.

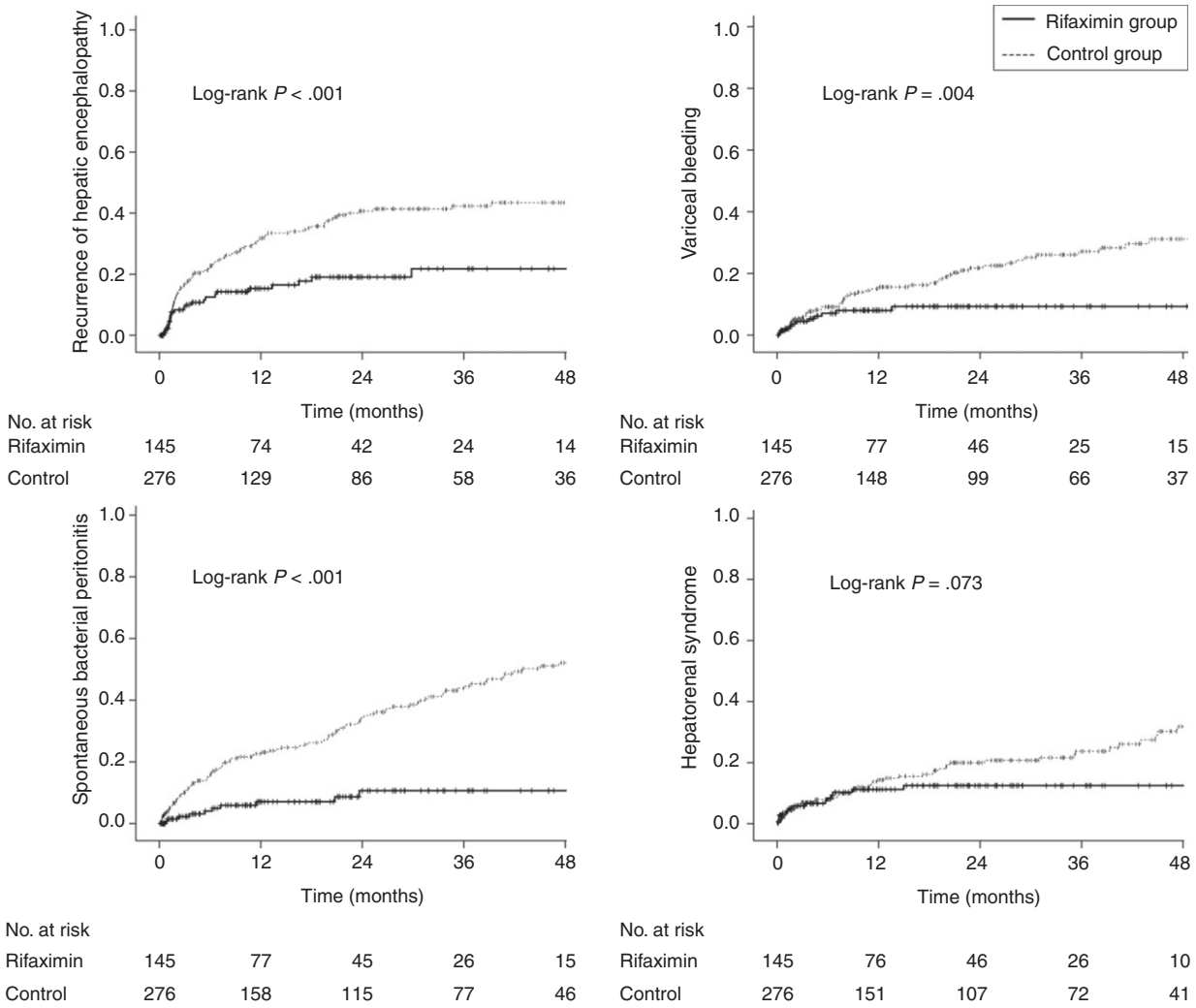


**FIGURE 3** Kaplan–Meier estimates of developing of secondary endpoints according to treatment group in the non-hepatocellular carcinoma (HCC) cohort. The solid lines represent results in the rifaximin group and the dotted lines represent results in the control group. In the non-HCC cohort, the rifaximin group showed significantly lower risks of recurrent HE (left upper panel), SBP (left lower panel) and variceal bleeding (right upper panel) than the control group. Patients who received rifaximin also had a lower risk of HRS (right lower panel) than patients who did not receive rifaximin, but the difference was not significant

## 4 | DISCUSSION

In our study, we investigated the overall effect of rifaximin in patients experiencing HE and found that rifaximin was associated with lower risk of death and risk of developing cirrhotic complications, including the recurrence of HE, SBP and variceal bleeding, in patients without HCC. Among patients with HCC, rifaximin was not associated with the risk of death, although it reduced the risk of developing SBP.

Our study demonstrated that rifaximin treatment was associated with lower risk of death in the non-HCC cohort, which was confirmed by both Cox proportional hazards models and inverse probability weighting. Until now, only several small short-term studies have reported the effect of rifaximin treatment in patients with cirrhosis. One study showed that the 5-year cumulative probability of survival was higher in patients receiving rifaximin (n = 23) than in patients not receiving rifaximin (n = 46).[25] These results are consistent with our study. However, that study had a small sample size and compared the rifaximin group with a placebo group, not a lactulose group, as in our study. In a previous study, efficacy of rifaximin for improving survival also was showed in patients with cirrhosis. A significant decrease in short-term mortality for 10 days after treatment was evident in patients who received lactulose plus rifaximin compared to patients who received lactulose alone.[26] The study was limited by a short-term follow-up period. In contrast, the median follow-up duration was 18.0 months in our study and we demonstrated rifaximin's effect on overall survival during a longer follow-up period than the previous study. We also evaluated the effect of rifaximin on survival in patients with HCC. Unlike the results in the non-HCC cohort, rifaximin treatment was not associated with the risk of death in the HCC cohort. There were no changes in the results after adjusting for TNM stage, which is known to be the most important prognostic factor in HCC.[27] This may indicate that the tumour itself has a greater impact on survival than cirrhotic complications in patients with HCC.

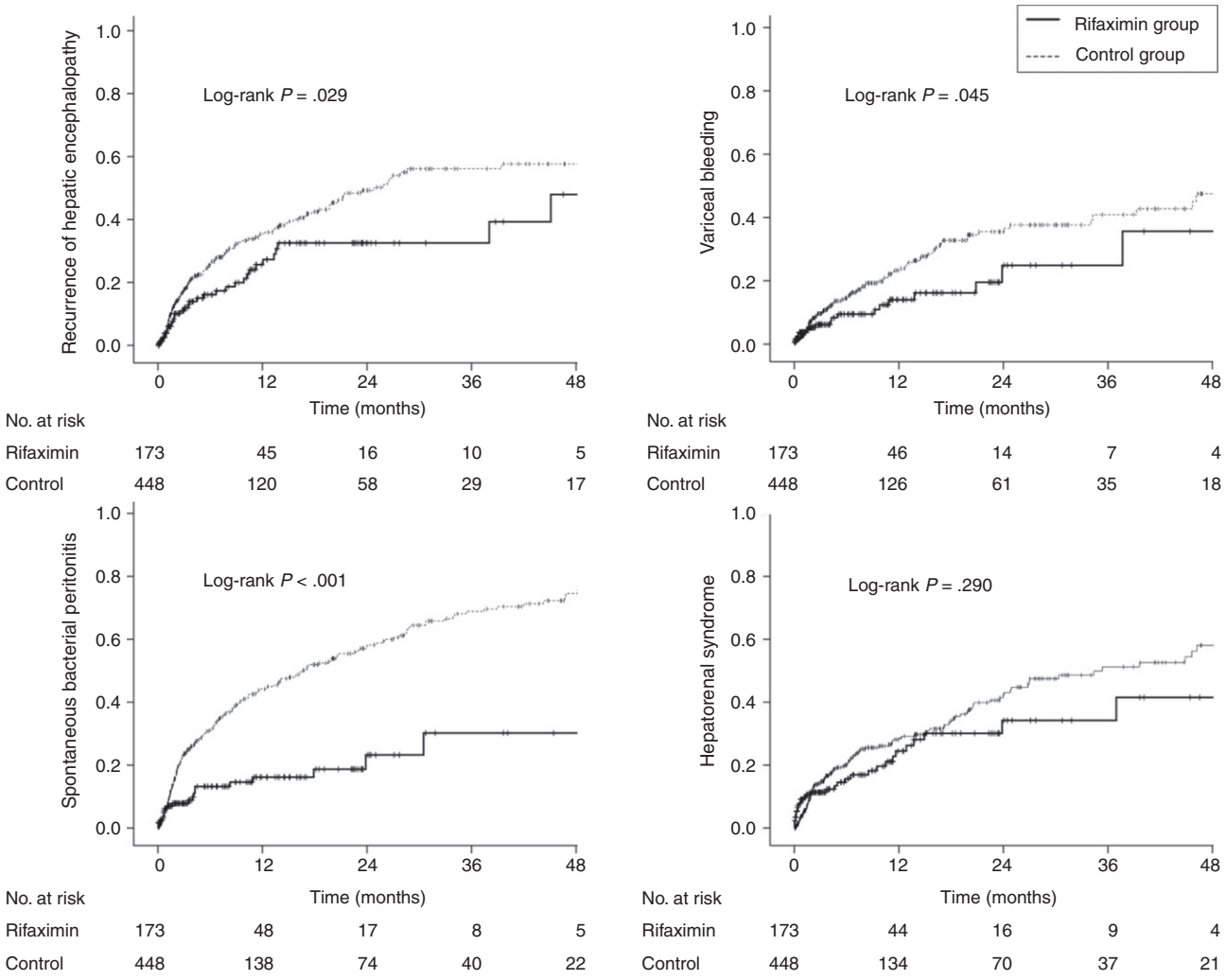


**FIGURE 4** Kaplan–Meier estimates of developing of secondary endpoints according to treatment group in the hepatocellular carcinoma (HCC) cohort. The solid lines represent results in the rifaximin group and the dotted lines represent results in the control group. In the HCC cohort, the rifaximin group showed significantly lower risks of recurrent HE (left upper panel), SBP (left lower panel) and variceal bleeding (right upper panel) than the control group. There was no significant difference in the risk of HRS (right lower panel) between the rifaximin group and the control group

Small intestinal bacterial overgrowth in cirrhotic patients is common and is associated with systemic endotoxemia, which leads to further worsening of portal hypertension.[28] In a previous study, concomitant rifaximin and lactulose significantly affected the mucosal microbiota composition compared with lactulose alone.[29] A prospective study also showed that rifaximin reduces levels of endotoxins, such as lipopolysaccharide, and improves systemic inflammation in cirrhotic patients.[30] These data suggest that rifaximin may contribute to the control of gut microbiota imbalance and act as an important therapeutic agent for controlling small intestinal bacterial overgrowth. These modulatory activities on gut microbiota bacterial composition may underline the efficacy of rifaximin for gut-derived toxins that contribute to the development of complications of cirrhosis.[31] This effect might improve liver hemodynamics and associate with lower risk of death.

In non-HCC cohort, our study clearly demonstrated that rifaximin had additive effects compared to lactulose alone for reducing the risks of recurrent HE and SBP. Small intestinal bacterial overgrowth and bacterial translocation are mainstays of SBP development. Therefore, it has been hypothesised that rifaximin, being effective on small intestine bacterial overgrowth, could be beneficial in preventing SBP. Indeed, our study also showed that lower risk of SBP was associated with rifaximin. Rifaximin treatment was also an independent factor for preventing variceal bleeding in our study. A previous study reported that rifaximin treatment reduced endotoxin levels and associated with a decreased hepatic venous pressure gradient.[31] It is well accepted that reduction in portal pressure (below 12 mm Hg) prevents variceal bleeding.[32,33] However, rifaximin was not confirmed to reduce the risk of HRS. Although rifaximin may reduce endotoxemia through a beneficial modulation of gut microbiota, rifaximin was not related with the risk of developing HRS, possibly because HRS has a multifactorial pathophysiology, except for endotoxemia.

In the HCC cohort, rifaximin treatment was less effective in reducing the risk of cirrhotic complications, except for SBP, than in the non-HCC group. The Child–Turcotte–Pugh score was not

significantly different between non-HCC group and HCC group in our study ($P = .158$). Previous studies reported that HCC was an independent factor that contributed to the poor prognosis of HE.[34,35] Concentrations of aromatic amino acids were reported to be higher in patients with HCC than in patients without HCC, which suggests that the imbalance of aromatic and branched amino acids are related to the development of HE in patients with HCC.[36] The presence of HCC was speculated to synergistically influence poor outcomes in HE and reduce the effect of rifaximin in preventing recurrent HE. Our study also showed that rifaximin treatment was not an independent negative risk factor for variceal bleeding in patients with HCC. We assume that portal vein thrombosis was distributed unevenly between patients with HCC and without HCC. Previous studies have associated the presence of portal vein thrombosis with negative outcomes in variceal bleeding.[37]

In our study, the impact of rifaximin treatment on overall survival of the non-HCC and HCC cohorts differed (Figure S1). The interaction plot indicated a significant interaction between the presence of HCC and the impact of treatment regimens on overall survival (Figure S2). In the entire cohort, the beneficial effect of rifaximin treatment on overall survival still remained even after consideration of the interaction. We evaluated the cost-effectiveness of rifaximin by calculating the NNT and the incremental costs per patient ($7440/year) relative to the control group. The 1-year incremental cost was $85 560 to increase the survival rate in one patient without HCC. The 1-year incremental cost ranged from $47 616 to $69 936 to prevent portal hypertension-related complications. Therefore, with consideration given to the economic situation of each country, rifaximin treatment can be recommended for patients with cirrhosis to decrease the costs incurred by most health care systems.

The major limitation of our study is that it was based on retrospective observational data. Thus, we performed the multivariate Cox regression analysis with and without inverse probability weighting to balance the baseline characteristics. After the multiple regression and inverse probability weighting analyses, rifaximin consistently showed significant associations with increased overall survival rates and reduced portal hypertension-related complications. Moreover, it may be unethical to launch a prospective clinical trial comparing rifaximin to a control group because rifaximin is already a standard treatment for patients who experience HE in clinical practice. Second, this study enrolled patients at high risk for portal hypertension-related complications who already had experienced HE and had advanced cirrhosis. Moreover, more than half of the patients with HCC (54.3%) had Child–Turcotte–Pugh class C cirrhosis and therefore in Barcelona Clinic Liver Cancer stage D. This might explain why our HCC study cohort experienced a higher incidence of endpoints, including a 65% mortality month 12, than reported in previous studies. There might be a selection bias because our study cohort consisted of patients at tertiary referral centre who had advanced or recurrent HCC, which are associated with worse outcomes. Our study could provide favourable evidence to launch a randomised clinical trial in patients who have decompensated liver cirrhosis and no previous HE event. The strengths of the present study include the fact that the data were obtained from a large number of patients. Although there was missing data including ECOG status known to be one of the important predictor of outcome in HCC patients in our retrospective observational study, this is the first study evaluating the effect of rifaximin in patients with HCC. Nevertheless, because this is a retrospective observational study, it could only demonstrate associations between rifaximin treatment and various clinical outcomes, including overall survival. Therefore, further studies, such as randomised prospective studies, are necessary to clarify the beneficial effects of rifaximin for patients with portal hypertension. In conclusion, the results of our study show that rifaximin treatment was significantly associated with lower risk of death and the risk of developing SBP, variceal bleeding and recurrent HE in patients without HCC. Although rifaximin was not associated with lower risk of death in patients with HCC, it has been shown to be related to preventing portal hypertension-related complications. This study may support the initiation of a large cohort study to assess the overall efficacy of rifaximin in patients with previous HE.

## ACKNOWLEDGEMENTS

*Declaration of personal interests*: None.

## AUTHORSHIP

*Guarantor of the article*: Jeong-Hoon Lee, MD, PhD.

*Author contributions*: Development of study concept and design: Seong Hee Kang, Yun Bin Lee, and Jeong-Hoon Lee. Collection and analysis of the data: Seong Hee Kang, Yun Bin Lee, Jeong-Hoon Lee, Joon Yeul Nam, Young Chang, Hyeki Cho, Jeong-Ju Yoo, Young Youn Cho, Eun Ju Cho, Su Jong Yu, and Moon Young Kim. Interpretation of the data: Seong Hee Kang, Yun Bin Lee, Jeong-Hoon Lee, Yoon Jun Kim, Soon Koo Baik, and Jung-Hwan Yoon. Drafting the manuscript: Seong Hee Kang, Yun Bin Lee, and Jeong-Hoon Lee. All authors approved the final version of the manuscript.

## ORCID

*J.-H. Lee* http://orcid.org/0000-0002-0315-2080
*Y. J. Kim* http://orcid.org/0000-0001-9141-7773

## LINKED CONTENT

This article is linked to Juang, Kang et al, Wang et al, and Borentain et al papers. To view these papers visit https://doi.org/10.1111/apt.14325, https://doi.org/10.1111/apt.14343, https://doi.org/10.1111/apt.14353 and https://doi.org/10.1111/apt.14516.

## REFERENCES

1. Prasad S, Dhiman RK, Duseja A, Chawla YK, Sharma A, Agarwal R. Lactulose improves cognitive functions and health-related quality of life in patients with cirrhosis who have minimal hepatic encephalopathy. *Hepatology*. 2007;45:549-559.

2. Mathers CD, Lopez AD, Murray CJL. The burden of disease and mortality by condition: data, methods, and results for 2001. In: Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL, eds. *Global Burden of Disease and Risk Factors*. Washington, DC: International Bank for Reconstruction and Development/The World Bank. 2006:68-72.
3. Minino AM, Xu J, Kochanek KD, Tejada-Vera B. Death in the United States. *NCHS Data Brief*. 2007;2009:1-8.
4. Garcia-Tsao G, Lim JK; Members of Veterans Affairs Hepatitis CRCP. Management and treatment of patients with cirrhosis and portal hypertension: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program. *Am J Gastroenterol*. 2009;104:1802-1829.
5. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol*. 2006;44:217-231.
6. Guan R, Lui HF. Treatment of hepatitis B in decompensated liver cirrhosis. *Int J Hepatol*. 2011;2011:918017.
7. Lo GH, Chen WC, Lin CK, et al. Improved survival in patients receiving medical therapy as compared with banding ligation for the prevention of esophageal variceal rebleeding. *Hepatology*. 2008;48:580-587.
8. Thiele M, Krag A, Rohde U, Gluud LL. Meta-analysis: banding ligation and medical interventions for the prevention of rebleeding from oesophageal varices. *Aliment Pharmacol Ther*. 2012;35:1155-1165.
9. Chen Y, Yang F, Lu H, et al. Characterization of fecal microbial communities in patients with liver cirrhosis. *Hepatology*. 2011;54:562-572.
10. Bajaj JS, Heuman DM, Hylemon PB, et al. Altered profile of human gut microbiome is associated with cirrhosis and its complications. *J Hepatol*. 2014;60:940-947.
11. Giannelli V, Di Gregorio V, Iebba V, et al. Microbiota and the gut-liver axis: bacterial translocation, inflammation and infection in cirrhosis. *World J Gastroenterol*. 2014;20:16795-16810.
12. Garcia-Tsao G, Lee FY, Barden GE, Cartun R, West AB. Bacterial translocation to mesenteric lymph nodes is increased in cirrhotic rats with ascites. *Gastroenterology*. 1995;108:1835-1841.
13. Wiest R, Garcia-Tsao G. Bacterial translocation (BT) in cirrhosis. *Hepatology*. 2005;41:422-433.
14. Soriano G, Guarner C, Teixido M, et al. Selective intestinal decontamination prevents spontaneous bacterial peritonitis. *Gastroenterology*. 1991;100:477-481.
15. Gerard L, Garey KW, DuPont HL. Rifaximin: a nonabsorbable rifamycin antibiotic for use in nonsystemic gastrointestinal infections. *Expert Rev Anti Infect Ther*. 2005;3:201-211.
16. Debbia EA, Maioli E, Roveta S, Marchese A. Effects of rifaximin on bacterial virulence mechanisms at supra- and sub-inhibitory concentrations. *J Chemother*. 2008;20:186-194.
17. Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med*. 2010;362:1071-1081.
18. Bajaj JS, Barrett AC, Bortey E, Paterson C, Forbes WP. Prolonged remission from hepatic encephalopathy with rifaximin: results of a placebo crossover analysis. *Aliment Pharmacol Ther*. 2015;41:39-45.
19. Jung KS, Kim SU, Ahn SH, et al. Risk assessment of hepatitis B virus-related hepatocellular carcinoma development using liver stiffness measurement (FibroScan). *Hepatology*. 2011;53:885-894.
20. Spence MM, Makarem AF, Reyes SL, et al. Evaluation of an outpatient pharmacy clinical services program on adherence and clinical outcomes among patients with diabetes and/or coronary artery disease. *J Manag Care Spec Pharm*. 2014;20:1036-1045.
21. Sjolander A. Propensity scores and M-structures. *Stat Med* 2009;28:1416-1420; author reply 20-3.
22. Curtis LH, Hammill BG, Eisenstein EL, Kramer JM, Anstrom KJ. Using inverse probability-weighted estimators in comparative effectiveness analyses with observational databases. *Med Care*. 2007;45:S103-S107.
23. Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology*. 2016;63:261-283.
24. Zhuang H. Updates of EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *Zhonghua Gan Zang Bing Za Zhi*. 2012;20:427-429.
25. Vlachogiannakos J, Viazis N, Vasianopoulou P, Vafiadis I, Karamanolis DG, Ladas SD. Long-term administration of rifaximin improves the prognosis of patients with decompensated alcoholic cirrhosis. *J Gastroenterol Hepatol*. 2013;28:450-455.
26. Sharma BC, Sharma P, Lunia MK, Srivastava S, Goyal R, Sarin SK. A randomized, double-blind, controlled trial comparing rifaximin plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy. *Am J Gastroenterol*. 2013;108:1458-1463.
27. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet*. 2012;379:1245-1255.
28. Bauer TM, Schwacha H, Steinbruckner B, et al. Small intestinal bacterial overgrowth in human cirrhosis is associated with systemic endotoxemia. *Am J Gastroenterol*. 2002;97:2364-2370.
29. Bajaj JS, Hylemon PB, Ridlon JM, et al. Colonic mucosal microbiome differs from stool microbiome in cirrhosis and hepatic encephalopathy and is linked to cognition and inflammation. *Am J Physiol Gastrointest Liver Physiol*. 2012;303:G675-G685.
30. Kalambokis GN, Mouzaki A, Rodi M, et al. Rifaximin improves systemic hemodynamics and renal function in patients with alcohol-related cirrhosis and ascites. *Clin Gastroenterol Hepatol*. 2012;10:815-818.
31. Vlachogiannakos J, Saveriadis AS, Viazis N, et al. Intestinal decontamination improves liver haemodynamics in patients with alcohol-related decompensated cirrhosis. *Aliment Pharmacol Ther*. 2009;29:992-999.
32. Groszmann RJ, Bosch J, Grace ND, et al. Hemodynamic events in a prospective randomized trial of propranolol versus placebo in the prevention of a first variceal hemorrhage. *Gastroenterology*. 1990;99:1401-1407.
33. Feu F, Garcia-Pagan JC, Bosch J, et al. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. *Lancet*. 1995;346:1056-1059.
34. Yoneyama K, Nebashi Y, Kiuchi Y, Shibata M, Mitamura K. Prognostic index of cirrhotic patients with hepatic encephalopathy with and without hepatocellular carcinoma. *Dig Dis Sci*. 2004;49:1174-1180.
35. Sharma P, Sharma BC, Sarin SK. Predictors of nonresponse to lactulose in patients with cirrhosis and hepatic encephalopathy. *Eur J Gastroenterol Hepatol*. 2010;22:526-531.
36. Watanabe A, Higashi T, Sakata T, Nagashima H. Serum amino acid levels in patients with hepatocellular carcinoma. *Cancer*. 1984;54:1875-1882.
37. Said A, Williams J, Holden J, et al. Model for end stage liver disease score predicts mortality across a broad spectrum of liver disease. *J Hepatol*. 2004;40:897-903.

## SUPPORTING INFORMATION

Additional Supporting Information will be found online in the supporting information tab for this article.

**How to cite this article:** Kang SH, Lee YB, Lee J-H, et al. Rifaximin treatment is associated with reduced risk of cirrhotic complications and prolonged overall survival in patients experiencing hepatic encephalopathy. *Aliment Pharmacol Ther*. 2017;46:845–855.
https://doi.org/10.1111/apt.14275