Managing Hepatic Encephalopathy - Combination of Lactulose and Rifaximin Versus Lactulose Monotherapy: A Systematic Review and Meta-analysis

Saad Khalid¹, Uzair Aslam¹, Iftikhar Haider Naqvi², Mahima Khatri¹, Mishal Shan Siddiqui¹ and Zoha Allahuddin^{1*}

Table A.1: Quality assessment of cohort studies by Newcastle-Ottawa scale.

Author	Cohort Represent- ability	Selection of Non exposed Cohort	Ascertain- ment of Expo- sure	Outcome Not Present at Baseline	Comparability of Cohorts for Important Factors	Comparability of Cohorts for Other Variables	Assess- ment of Outcome	Follow- Up Long Enough for Outcome to Occur	Adequacy of Follow- Up	Quality
Courson 2015 [1]	*	*	*	*	*	*	*	*		Good
Kang 2017 [2]	*	*	*	*	*		*	*		Good
Ahire 2017 [3]	*	*	*	*		*	*	*		Good
Bajaj 2019 [4]	*	*	*	*	*		*	*		Good
Poudyal 2019 [5]	*	*	*	*	*	*	*	*		Good
Chang 2021 [6]	*	*	*	*	*		*	*	*	Good

Table A.2: Quality assessment of Randomized Controlled Trials by Cochrane Risk of bias tool.

	Select	ion Bias	Performance Bias	Detection bias	Attrition bias	Reporting Bias	Other bias		
Article	Random Sequence Generation Allocation concealment		Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting	Anything else, ideal- ly prespec- ified	Our evaluation	
Sharma 2013 [7]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality	
Haq 2014 [8]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Poor quality	
Butt 2018 [9]	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Fair quality	
Hasan 2018 [10]	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Fair quality	
Shafique Ahmed 2018 [11]	Low risk	Unclear risk	High risk	High risk	Low risk	Unclear risk	Low risk	Poor quality	
Shoaib Ahmed 2018 [12]	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Poor quality	
Hussain 2020 [13]	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Poor quality	

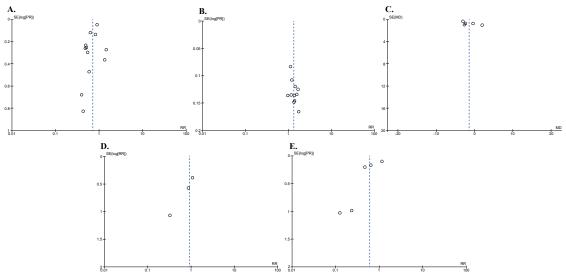


Fig A.1: Funnel plots for all outcomes. (A) Mortality (B) Clinical Efficacy (C) Length of stay (D) Adverse effects (E) HE recurrence

Table A.3: Results of Egger test for publication bias of all outcomes.

Outcome	Eggers's test
Mortality	0.7913
Clinical efficacy	0.0004
Length of stay	0.1020
Adverse effects	0.4167
HE recurrence	0.2297

REFERENCES

- Courson A, Jones GM, Twilla JD. Treatment of Acute Hepatic Encephalopathy: Comparing the Effects of Adding Rifaximin to Lactulose on Patient Outcomes. J Pharm Pract 2016;29(3):212– 217. https://doi.org/10.1177/0897190014566312.
- Kang SH, Lee YB, Lee JH, Nam JY, Chang Y, Cho 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(9):845–855. https://doi.org/10.1111/apt.14275.
- Ahire K, Sonawale A. Comparison of Rifaximin Plus Lactulose with the Lactulose Alone for the Treatment of Hepatic Encephalopathy. J Assoc Physicians India 2017;65(8):42-6.
- Bajaj JS, O'Leary JG, Tandon P, Wong F, Kamath PS, Biggins SW, et al. Targets to improve quality of care for patients with hepatic encephalopathy: data from a multi-centre cohort. Aliment Pharmacol Ther 2019;49(12):1518-1527. https://doi.org/10.1111/ apt.15265.
- Poudyal NS, Chaudhary S, Kc S, Paudel BN, Basnet BK, Mandal A, et al. Precipitating Factors and Treatment Outcomes of Hepatic Encephalopathy in Liver Cirrhosis. Cureus 2019;11(4):e4363. https://doi.org/10.7759/cureus.4363.
- Chang C, Huang CH, Tseng HJ, Yang FC, Chien RN. Real-World Experience of the One- Year Efficacy of Rifaximin Add-On to

- Lactulose Is Superior to Lactulose Alone in Patients with Cirrhosis Complicated with Recurrent Hepatic Encephalopathy in Taiwan. J Pers Med 2021;11(6):478. https://doi.org/10.3390/jpm11060478.
- 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(9):1458–63. https://doi.org/10.1038/ajg.2013.219.
- Miu H, Salim A, Afzal MS, Malik K, Amin J, Butt AK. Comparison of Rifaximin and Lactulose With Lactulose Alone in the Treatment of Acute Hepatic Encephalopathy in Patients With Liver Cirrhosis[J] Proceeding S.Z.P.G.M.I 2014;28(2):115–9.
- Butt NI, Butt UI, Kakar AATK, Malik T, Siddiqui AM. Is Lactulose Plus Rifaximin Better than Lactulose Alone in the Management of Hepatic Encephalopathy?. J Coll Physicians Surg Pak 2018;28(2):115-117. https://doi.org/10.29271/jcpsp.2018.02.115.
- Hasan S, Datta S, Bhattacherjee S, Banik S, Saha S, Bandyopadhyay D. A Randomized Controlled Trial Comparing the Efficacy of a Combination of Rifaximin and Lactulose with Lactulose only in the Treatment of Overt Hepatic Encephalopathy. J Assoc Physicians India 2018;66(1):32-36.
- Ahmed S, Ahmad S, han SU. Lactulose alone versus Lactulose+ Rifaximin for the management of Hepatic Encephalopathy. Pakistan J Medical Health Sci 2018;12(3):1269-71.
- Ahmed RS, Adnan M, Jabeen H. Efficacy of Lactulose Vs Lactulose with Rifaxamin in patients with Hepatic Encephalopathy: A Randomized Control Trial. Journal of Muhammad Medical College, Mirpurkhas 2018;9(1):39-41.
- Hussain T, Sattar M, Mustafa S, Batool U, Iqbal S, Hassan B. Comparing efficacy of Rifaximin plus Lactulose vs. Lactulose alone in treating Hepatic Encephalopathy. J Rawalpindi Med Coll 2020;24(4):339-43. https://doi.org/10.37939/jrmc.v24i4.1418.