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

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Abstract

Background: Hepatic Encephalopathy (HE), a neuropsychiatric complication of hepatic failure, is currently managed with lactulose as first-line treatment followed by other adjuncts if needed. In this meta-analysis, we determined the effect of lactulose and rifaximin combination in terms of efficacy and mortality reduction compared to lactulose alone.

Materials and Methods: We searched databases (PubMed, BioMed Central, and Cochrane-Central) until July, 2022 for original studies inspecting the effects of Rifaximin and Lactulose (combination therapy) vs. lactulose as a monotherapy in the treatment of HE on outcomes of clinical efficacy, hospital stay length, HE recurrence, drugs' side effects and mortality. Data was analyzed *via* Review Manager (version5.4.1) and OpenMetaAnalyst. Relative risks (RR) and weighted mean differences (WMD) with 95% confidence intervals were calculated.

Results: Fifteen studies with 4327 patients were included. Pooled analysis showed combination therapy to be associated with a significantly lower mortality rate in patients having HE when compared to lactulose alone (RR 0.71 95% CI 0.58-0.88, P=0.002, I2= 68%), and clinical efficacy was also improved in the combination group (RR 1.33, 95%CI 1.19-1.48, P <0.00001, I2= 52%). HE recurrence rate, adverse events, and length of hospital stay did not significantly differ among the two groups (RR= 0.61, 95 % CI= 0.35 to 1.05, P= 0.08, I2= 84%), (RR= 0.92, 95% CI= 0.51 to 1.69, P= 0.80, I2 = 0) and (WMD −1.52, 95% CI −3.22 to 0.18, P=0.08, I2 = 83%) respectively.

Conclusion: Combination therapy shows survival benefit and superior clinical efficacy over lactulose monotherapy in managing hepatic encephalopathy.

Keywords: *Hepatic encephalopathy, Rifaximin, Lactulose, Meta-analysis, systematic review.*

INTRODUCTION

Hepatic encephalopathy (HE) is a fatal but potentially reversible neuropsychiatric syndrome caused by hepatic inability to detoxify neurotoxins, including ammonia derived from the action of intestinal bacteria due to hepatic insufficiency and/or portosystemic shunting [1, 2]. The toxic chemicals concentrate in the systemic circulation, diffuse across the blood-brain barrier and alter neurotransmission [3]. Consequently, a wide range of neuropsychiatric symptoms develops extending from subtle to severe altered behavior, cognition, sleep, and psychomotor function to coma and death [1, 4].

HE is a devastating complication of liver decompensation of acute and chronic liver failure with prevalence and severity dependent on liver function status. Overt HE is reported 10-14% at first presentation of cirrhosis. Moreover, patients with advanced cirrhosis and having transjugular intrahepatic portosystemic shunt (TIPS) have shown HE in 16-21% and 10-50% respectively [1]. HE is a significant contributor to mortality in cirrhotics, with one study estimating the survival to be 43% and 23% at 1 and 3 years, respectively, for patients who developed severe HE (West Haven Criteria grade 3 and 4) [5].

Thus, early, effective and aggressive management of this complication is of crucial importance to improve survival, decrease the demand for liver transplantation and reduce the burden on patients and healthcare. Although liver transplantation offers the best treatment for refractory and recurrent HE [1], this therapeutic option is limited due to an existing organ shortage. The management of HE is initiated with recognition and rectification of different precipitating factors such as GI bleeding, constipation, electrolyte imbalance, infections, worsening liver function, renal insufficiency, and use of sedatives. This alone will result in resolution in about 90% of cases [6]. Furthermore, most patients have high serum ammonia levels, and ammonia reduction therapy with non-absorbable disaccharides (NAD), antibiotics, branched-chain amino acids (BCAA), and L-ornithine-L-aspartate (LOLA) is performed. Current guidelines recommend lactulose as the initial drug of choice [1]. However, inadequate response or intolerance to lactulose prompts the addition of rifaximin or other poorly absorbed antibiotics that alter the gut microbiota and decrease the number of nitrogen-producing bacteria

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[7]. It is plausible that this approach can undertreat the patients and/or delay the adequate treatment in lactulose poor responders. This can particularly impact survival in patients with higher grades of HE. Hence, dual therapy may be superior to monotherapy.

The comparison of dual therapy in HE, where lactulose alone or with rifaximin has shown conflicting results in various observational studies and randomized control trials (RCT's) [8-10]. An earlier comprehensive meta-analysis has shown better efficacy and mortality with combination treatment than lactulose alone [11]. However, after the addition of newer studies in the literature, it is imperative to consider those studies in evidence synthesis and to determine the strength of effect either of the treatment options possesses. Therefore, this study was aimed to perform a thorough systematic review and meta-analysis to compare the efficacy, adverse effects, length of hospital stay, HE recurrence, and mortality in patients receiving lactulose alone *versus* rifaximin plus lactulose for HE of any severity and etiology.

METHODOLOGY

The current meta-analysis is performed in agreement with the guidelines provided by PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) [12]. The meta-analysis was not registered with any registry.

Literature Search and Article Selection

A systematic literature review was carried out on PubMed, Cochrane Central and BioMed Central databases since their inception up till July 2022 with the keywords and corresponding MeSH terms listed below:

(Hepatic Encephalopathy OR Hepatic Encephalopathies OR Portal Systemic Encephalopathy OR Portal-Systemic Encephalopathies OR Portosystemic Encephalopathy OR Portosystemic Encephalopathies OR Hepatocerebral Encephalopathy OR Hepatocerebral Encephalopathies OR Portal-Systemic Encephalopathy OR Hepatic Coma OR Hepatic Comas OR Hepatic Stupor OR Hepatic Stupors OR Fulminant Hepatic Failure with Cerebral Oedema) AND (Lactulose OR Duphalac OR Normase OR Amivalex) AND (Rifaximin OR L 105 OR L-105 OR L105 OR Redactiv OR Xifaxan OR 4-Deoxy-4'-methylpyrido(1',2'-1,2)imidazo(5,4C)rifamycin).

Two reviewers (SK and UA) independently screened the results. The third reviewer's (MK) opinion was sought if discrepancies were found. Studies were first shortlisted on the basis of title and abstract followed by full-text screening. The references of included studies were also screened for relevant articles. Only the manuscripts published in English language were considered.

Study Inclusion and Exclusion Criteria

The studies were included if: (1) Full text was published in English language or the conference abstract was included in the previous meta-analysis on the similar topic, (2) Randomized Controlled Trials (RCTs) and Cohort studies were included (3) Study population comprised of adult patients with any grade of hepatic encephalopathy secondary to liver disease, (4) Comparison was drawn between Rifaximin + Lactulose vs. the use of lactulose alone for relevant outcomes). No restriction was made based on dosage of either Rifaximin or Lactulose, or the type of control used (simple control or placebo). Review articles, editorials, case-reports, study protocols, and non-comparative studies were excluded.

Data Extraction

Data extraction for baseline variables and outcomes was completed by all 4 reviewers (SK, UA, MSS, MK). Extracted information consisted of the first author, publication year, type of study (observational/ randomized controlled trial), total number of patients, number of patients receiving Rifaximin + Lactulose and the number of patients receiving lactulose, either alone or with placebo. Baseline characteristics included demographics of age, gender distribution, along with West Haven Clinical Severity Grade of HE (Grade I-IV) and type of HE (overt vs. covert), Child-Turcotte-Pugh (CTP) score with class (CTP-A,CTP-B, CTP-C), Model for End-Stage Liver Disease (MELD) score, etiology of liver disease, HE index and grade of mental status *via* the Conn's modification of the Parsons-Smith classification (Grade I-IV). Doses of the administered drugs, treatment duration, previous history of HE, prior use of lactulose, duration of cirrhosis, and presence of ascites were also recorded. Baseline laboratory parameters of blood urea, blood ammonia, liver enzymes, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, serum albumin, prothrombin time, international normalized ratio (INR), hemoglobin, platelet count, creatinine, and electrolytes (Na+, K+) were also extracted. Precipitating factors for the current episode of HE along with the need of inotropic support or fresh frozen plasma (FFP) were likewise recorded.

Primary outcomes of in-hospital mortality, clinical efficacy as determined by reversal events, and improvement in the grade of HE, HE recurrence events, and the length of hospital stay were extracted after searching through the full text and tables of selected studies. Secondary outcomes included adverse effects of drugs (diarrhea, abdominal pain), adverse events such as the development of spontaneous bacterial peritonitis (SBP), variceal bleeding *etc.*, blood ammonia levels, mental status grade, grade of asterixis, and scale used for number connection.

Calculation of the Risk of Bias

Quality assessment of all observational studies included in the meta-analysis was conducted by Newcastle-Ottawa scale. Cochrane risk-of-bias tool was applied for quality assessment of randomized controlled trials included in meta-analysis [13, 14].

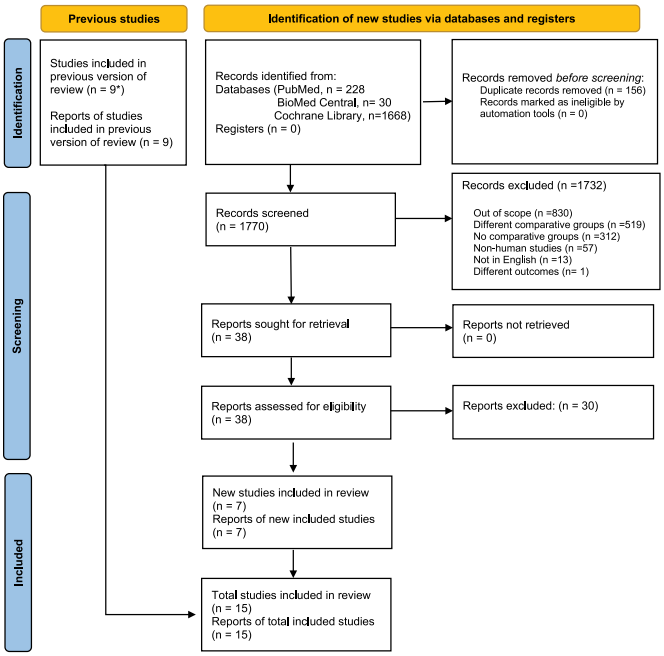


Fig. (1): PRISMA Flow diagram.

Data Analysis

Comparative studies were statistically analyzed by using Review Manager Version 5.4.1 and OpenMetaAnalyst. RR (relative risk) were calculated with 95% confidence intervals (CIs) and the pooling of results were done through random-effects model used for dichotomous data. The results were displayed by forest plots. Publication bias were analyzed by using Egger's test and funnel plots were made accordingly. Higgin's I^2 test was used for determination of heterogeneity and interpreted as low heterogenicity if <25%, considered moderate heterogenicity if between 25-75%, and labelled as high heterogenicity when >75% [15]. Furthermore, a univariate meta- regression was done to determine the corelation amongst the outcomes of clinical efficacy and mortality on the age and gender of patients suffering from HE. Statistical significance was considered with P-value of <0.05

RESULTS

The preliminary literature search yielded a total of 1926 articles. On screening by title and abstract and after removal of identical studies, seven new studies were identified. Finally, fifteen studies [8-10, 16-27] were included for analysis where full text was available and abstracts of two studies were also included; among all studies one study separated patients into two cohorts (having HCC or no HCC) [16] which were considered as two separate trials. A thorough search in accordance with PRISMA has been shown in the flowchart (**Fig. 1**).

Characteristics of Participants

In the combination group (rifaximin and lactulose), 2025 patients were assigned, whereas, 2302 patients were allotted to the control group (lactulose alone). Demographic profiles and clinical characteristics have shown in Table **1**. Overt HE (based on West Haven criteria, ≥ grade 2) were covered in nine studies [8-10, 16-21], whereas recurrent and new-onset HE in patients without a applying full West Haven criteria were found in three studies. [16, 17, 22] The causes of cirrhosis included chronic hepatic virus (HBV and HCV), alcohol and others, and it was found that viral infection had a very high association with HE (270/4609). The above-mentioned HE grade judged the severity of HE. The

Table 1: Baseline characteristics of the studies included in the meta-analysis.

Study	Design	Type	Case n1/n2	Age in years Mean ± SD	Males n(%)	HE Type	HE Severity	Etiology of CLD n(%)	Dosage	Treatment duration in days	Follow up duration in days
Gao 2012 [25]	RCT	N/A	31/ 31	58/61	22(71)/ 19(61.3)	HE	Not reported	Not Reported	RFX 550mg BID + LA 60mL TID/LA 60ml TID	10–15	10–15
Sharma 2013 [17]	vRCT	Full text	63/ 57	40.4±8.5 / 37.5±10.5	47 (74.6) / 42 (73.7)	Overt	HE grade (2, 3, 4 ;%): 15.9, 31.7, 52.4 /21, 35, 43.9, CTP score: 9.9 ± 2.8 / 9.4 ± 2.5 CTP class (B, C; %): 24.1,75.9 / 29.8,70.2. MELD ($\bar{x}$ ± SD): 24.9 ± 6.6 / 23.8 ± 5.18	Alcohol: 40(63.4) / 32(56.1) HBV: 10(15.9) / 12(21.1) HC V: 3(4.8) / 4(7) Other: 10 (15.9) / 9(15.8)	RFX 400mg OD +LA 30- 60ml TID / LA 30-60ml + placebo TID	≤10	Until discharge
Gill 2014 [18]	RCT	Abstr act	100/ 100	40	70 (70)/ 70 (70)	Overt	HE grade (2, 3, 4 ;%): 60,70,70	Not Reported	RFX 550 mg BID + LA 30-60 ml BID or TD / LA 30-60 ml BID or TID + placebo	10	Until discharge

Study	Design	Type	Case n1/n2	Age in years Mean ± SD	Males n(%)	HE Type	HE Severity	Etiology of CLD n(%)	Dosage	Treatment duration in days	Follow up duration in days
Haq 2014 [19]	RCT	Full text	80/ 80	41±8.9 / 41±8.9	44 (55)/ 44 (55)	Overt	CTP class (A, B, C; %): 1.25, 26.25 , 72.5 / 0, 35, 65	Alcohol: 3 (1.8); HBV: 7 (4.3) HCV: 139 (86.8) Others: 11 (7.9)	RFX 550 mg BID + LA 30 ml TID / LA 30 ml TID	≤7	7
Courson 2015 [22]	RC	Full text	62/ 87	58±11 / 59±12	36(58.1)/ 54(61.2)	HE	MELD; Med (IQR): 21 (16-27) / 18 (14-24)	Alcohol: 27 (43.5) /52 (59.8), HBV: 1 (1.6) / 4 (4.6), HCV: 6 (9.7) / 16 (18.4), NASH: 19 (30.6) / 5 (5.7), HCC: 3 (4.8) / 9 (10.3), Others: 13 (20.9) / 23 (26.4)	RFX 550 mg BID + LA variable dose BID or TID/ LA variable dose BID or TID	≤10	180
Kang (HCC cohort) 2017 [16]	ROS	Full text	173/ 448	63.28±9.8/ 64.23±9.9	143 (82.6) / 351 (78.3)	Overt	CTP score: 9/10 CTP class (A, B, C; %): 2.3, 47.9, 49.7 / 2.2, 41.7 ,56	Alcohol: 24 (13.9) / 59 (13.2), Viral: 134 (77.4) / 353 (78.7), Others: 15 (8.7) / 36 (8.0)	RFX 600 mg BID+ LA 30- 60 mL TID/ LA 30-60 ml TID	Not reported	133.8 (39.5-498.8)
Kang (non- HCC cohort) 2017 [16]	ROS	Full text	145/276	58.6±11.5/ 60.2±12.0	92 (63.4) / 167 (60.5)	Overt	CTP score: 10/10 CTP class (A, B, C; %): 4.8, 43.4, 51.7 / 2.9, 40.2, 56.8	Alcohol: 55 (37.9) / 90 (32.6) Viral: 64 (44.1) / 126 (45.6) Others: 26 (17.9) / 60 (21.7)	RFX 600 mg BID+ LA 30- 60 mL TID/ LA 30-60 ml TID	Not Reported	547.5 (130.8-1104.1)
Ahire 2017 [9]	POS	Full text	32/ 28	49.5±9.7/ 53.9±10.2	28(87.5) / 26 (92.9)	Overt	HE grade (2, 3, 4 ;%): 31.25, 56.25,12.5 / 46.4,39.3,14.3 CTP class (A, B ,C; %):3.1, 18.8, 78.1 / 3.6 ,32.1 ,64.3	Alcohol: 23/15; HBV: 5/5; HCV: 4/4;	RFX 400 mg TID+LA 30-60ml TID/LA 30-60ml TID	7-15	7-15
Hasan 2018 [8]	RCT	Full text	45/ 46	44.7±10.6/ 44.9±10.1	36 (80)/ 38(82.6)	Covert & Overt	Not reported	Alcohol: 42 (93.3) / 39 (84.8) Others: 3 (6.7) / 7 (15.2)	RFX 400 mg TID+LA 15-30 ml QID/ LA 15-30 ml QID	≤10	≤10
Shoaib 2018 [27]	RCT	Full text	50/ 50	51.25±9.04/ 46.73 ±9.13	Not Reported	Covert & Overt	HE grade (1, 2, 3, 4 ;%): 4, 8, 38, 50 / 4,12, 44, 40 CTP class (A, B ,C; %): 6, 44, 50 / 8, 40, 52	Not Reported	RFX 550 mg TID+LA 20-100ml BID/ LA 20-100 ml BID	7	7
Shafique Ahmed 2018 [24]	RCT	Full text	60/ 60	54.1±9.8/ 53.2±10.6	34(56.7)/ 32(53.4)	Covert & Overt	HE grade (1, 2, 3, 4 ;%): 3.3, 20, 50, 26.7 / 6.7, 16.7, 43.3, 33.3 CTP class (A, B ,C; %): 3.3, 20, 76.7 / 1.7, 16.7, 81.7	HCV = 90 (75) HBV = 16 (13.3) Others: 14 (11.7)	RFX 550 mg BID + LA 30 ml TID / LA 30 ml TID	3	3

Study	Design	Type	Case n1/n2	Age in years Mean ± SD	Males n(%)	HE Type	HE Severity	Etiology of CLD n(%)	Dosage	Treatment duration in days	Follow up duration in days
Butt 2018 [10]	RCT	Full text	65/ 65	56.06±11.2/ 56.06±11.2	69(46.9)	Overt	HE grade (2, 3, 4 ;%): 40, 36.9, 23 / 26.1, 38.5, 35.4	Not Reported	RFX 550mg BID+LA 30ml TID/LA 30ml TID	10	10
Poudyal 2019 [20]	CS	Full text	44/ 44	48.20±0.69 / 48.68±9.00	37(84)/ 29 (66)	Covert & Overt	HE grade (1, 2, 3, 4 ;%): 15.9, 63.6, 18.2, 2.3 / 36.4, 47.7, 15.9, 0 CTP class (B ,C; %): 40.9, 59.1 / 20.5, 70.5	Alcohol: 36(81.8) / 39 (88.6) HBV: 3(6.8%) / 3(6.8%) HCV: 3(6.8%) / 1 (2.3) Others: 2 (4.6) / 1 (2.3)	RFX 550 mg BID+LA 30-60 ml TID/ LA 30-60 ml TID	Until death or discharge	Until discharge
Bajaj 2019 [21]	Cohort	Full text	859/ 695	57.30±9.42/ 57.23±10.11	532(62)/ 431(62)	Overt	CTP score; Med (IQR): 10.24 (1.97) / 9.86 (2.08) MELD ($\bar{x}$ ± SD): 21.30 ± 7.66 / 19.41 ± 7.65	Alcoholic cirrhosis: (29) / (37), HCV: (22) / (19) HCV + Alcoholic cirrhosis: (15) / (15) NASH: (24) / (17), Others: (11) / 1(2)	Not Reported	Until discharge	90
Hussain 2020 [23]	RCT	Full text	62/ 62	45.18±15.2 45.18±15.2	29 (46.77) / 40 (64.51)	Covert & Overt	HE grade (1, 2, 3, 4 ;%): 11.3, 19.4, 33.9, 35.5 / 4.8, 21, 35.5, 38.7	Not Reported	RFX 550mg BID+LA 30ml TID/LA 30ml TID	7	7
Chang 2021 [26]	RC	Full text	12/ 31	67±7.95/ 57.58±12.28	6(50)/ 20(64.5)	HE	HE grade (Min,1, 2, 3, 4 ;%): 33.3, 16.7, 33.3, 16.7, 0 / 0, 19.4, 48.4, 29, 3.2 MELD ; Med (IQR) : 14.05 (11.87–16.55) / 17.0 (14.0–22.0)	Not Reported	RFX 550 mg BID + LA 30- 45 mL BID-QID/ LA 30-45 mL BID-QID	Not Reported	365

Abbreviations: RCT: Randomized Controlled Trial, ROS: Retrospective Observational Study, POS: Prospective Observational Study, RC: Retrospective Cohort, CS: Cross-Sectional, CLD: Chronic Liver Disease, CTP: Child–Turcotte–Pugh, MELD: Model for End- stage Liver Disease, RFX: Rifaximin, LA: Lactulose, HBV: Hepatitis B Virus, HCV: Hepatitis C Virus, NASH, Nonalcoholic Steatohepatitis, OD: Once daily, BID: Twice daily, TID: Thrice daily, QID: Four times daily.

severity of underlying liver cirrhosis was determined by using the model for end-stage liver disease (MELD) score and CTP score. The mean MELD score was 17.525 ± 7.6 in the combination group and 20.542 ± 7.3 in the control group. Overt HE (apathy or lethargy, disorientation in time and personality changes) was diagnosed if HE grade was >1. In all these studies fixed dose of rifaximin was given where, 1100 mg dose being used in ten studies [10, 18, 19, 20-27], however 1,200 mg dose were used in four studies [8, 9, 16, 27], and one study used 400 mg once daily [17]. The dose of lactulose varied from 60 mL to 180 mL, where each ml contains 667 mg. Treatment duration was 10 or less than 10 days [25] in most of the studies however, a maximum treatment period of 2 weeks was reported in only one study. As the outcomes were mainly measured during hospital stay which has shown similar follow-up period for treatment duration with mortality and clinical efficacy analysis, whereas three studies had shown a >180 days follow-up period [16, 22, 26].

Quality Assessment

The assessment of quality of observational studies showed a low risk of bias among included studies (by using the New Castle Ottawa scale). However, quality assessment of RCTs found a high risk of bias in only four studies by using Cochrane risk of bias tool. **(Suppl Appendix A, Table A.1 and A.2).**

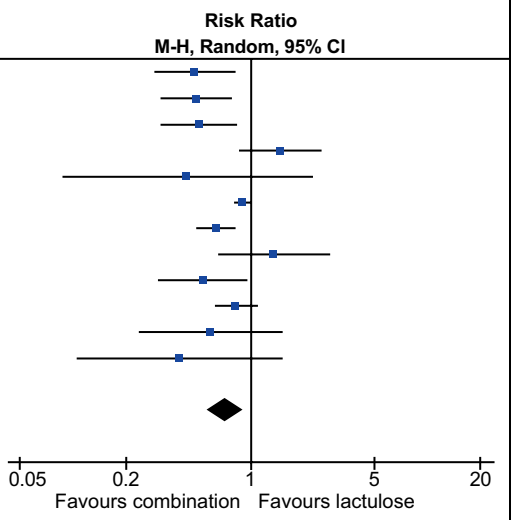
Mortality Outcome

Mortality data were reported in eleven studies [8, 9, 16-21, 22, 26, 27]. Pooled analysis has shown combination therapy was associated with a significantly low mortality rate in patients with HE when related with lactulose

A

Study or Subgroup	Combination Events	Combination Total	Lactulose Events	Lactulose Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Sharma	15	63	28	57	8.5%	0.48 [0.20, 0.81]	2013
Gill	20	100	40	100	9.5%	0.50 [0.32, 079]	2014
Haq	17	80	33	80	8.8%	0.52 [0.31, 0.85]	2014
Courson	20	62	19	87	8.2%	1.48 [0.86, 2.53]	2015
Ahire	2	32	4	28	1.6%	0.44 [0.09, 2.21]	2017
Kang-a	130	173	371	448	16.5%	0.91 [0.82, 1.00]	2017
Kang-b	53	145	157	276	14.1%	0.64 [0.51, 0.82]	2017
Hasan	13	45	10	47	5.8%	1.36 [0.66, 2.78]	2018
Shoaib Ahmed	12	50	22	50	7.4%	0.55 [0.30, 0.98]	2018
Bajaj	95	859	92	695	13.4%	0.84 [0.64, 1.09]	2019
Poudyal	6	44	10	44	4.0%	0.60 [0.24, 1.51]	2019
Chang	2	12	13	31	2.2%	0.40 [0.10, 1.50]	2021
Total (95% CI)		**1665**		**1943**	**100.0%**		
Total events	385		799				

Heterogenelty. Tau² = 0.07, Chi² = 34.08, df = 11 (P = 0.0004); P = 68%
Test for overall effect: Z = 3.12 (P = 0.002)



B

Study or Subgroup	Combination Events	Combination Total	Lactulose Events	Lactulose Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.6.1 RCTs							
Sharma	15	63	28	57	8.5%	0.48 [0.29, 0.81]	2013
Gill	20	100	40	100	9.5%	0.50 [0.32, 079]	2014
Haq	17	80	33	80	8.8%	0.52 [0.31, 0.85]	2014
Hasan	13	45	10	46	5.8%	1.33 [0.85, 2.72]	2018
Shoaib Ahmed	12	50	22	50	7.4%	0.55 [0.30, 0.98]	2018
Subtotal (95% CI)		**338**		**333**	**40.0%**	0.58 [0.43, 0.79]	
Total events	77		133				

Heterogenelty. Tau² = 0.04; Chi² = 6.26, df = 4 (P = 0.18); P = 36%
Test for overall effect: Z = 3.52 (P = 0.0004)

1.6.2 Observational studies							
Courson	20	62	19	87	8.2%	1.48 [0.86, 2.53]	2015
Kang-a	130	173	371	448	16.5%	0.91 [0.82, 1.00]	2017
Kang-b	53	145	157	276	14.1%	0.64 [0.51, 0.82]	2017
Ahire	2	32	4	28	1.6%	0.44 [0.09, 2.21]	2017
Poudyal	6	44	10	44	4.0%	0.60 [0.24, 1.51]	2019
Bajaj	95	859	92	695	13.4%	0.84 [0.64, 1.09]	2019
Chang	2	12	13	31	2.2%	0.40 [0.10, 1.50]	2021
Subtotal (95% CI)		**1327**		**1609**	**60.0%**	**0.82 [0.66, 1.02]**	
Total events	308		666				

Heterogenelty. Tau² = 0.04; Chi² = 14.56, df = 6 (P = 0.02); P = 59%
Test for overall effect: Z = 1.78 (P = 0.07)

Total (95% CI)		**1665**		**1942**	**100.0%**	**0.71 [0.58, 0.88]**	
Total events	385		799				

Heterogenelty. Tau² = 0.07; Chi² = 33.95, df = 11 (P = 0.0004); P = 68%
Test for overall effect: Z = 3.13 (P = 0.002)
Test for subgroup differences: Chi² = 3.26, df = 1 (P = 0.07), P = 69.3%

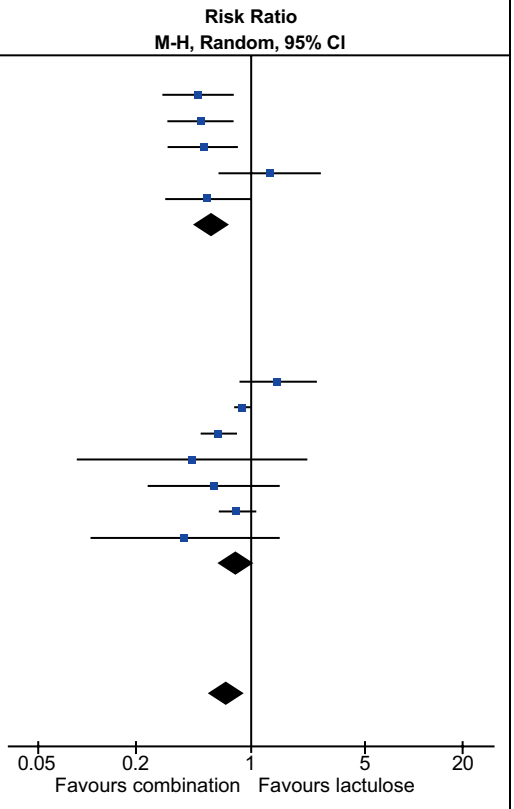


Fig (2): Forest plot for mortality **(A)** Pooled analysis of all studies, **(B)** Subgroup analysis of Randomized and non-randomized studies.

CI, confidence interval; M-H, Mantel-Haenszel; IV, inverse variance

treatment alone (RR 0.71 95% CI 0.58 to 0.88, P=0.002) with significant heterogeneity was found (I2=68%) (**Fig. 2**).

Among RCT'S the pooled analysis of five studies [8, 17-19, 26] having 671 patients have shown a significant decrease of mortality in patients having lactulose and rifaximin (combination therapy) (RR 0.58, 95% CI 0.43 to 0.79, P=0.0004, I2=36%) (**Fig. 2**).

Clinical Efficacy

Eleven studies reported the data of clinical efficacy [8-10, 17-20, 23-26]. Pooled analysis has shown combination therapy was associated with a significantly clinical efficacy in patients having HE when compared with lactulose treatment alone (RR 1.33, 95% CI 1.19 to 1.48, P = <0.00001). The heterogeneity was found (I2=52%) (**Fig. 3**).

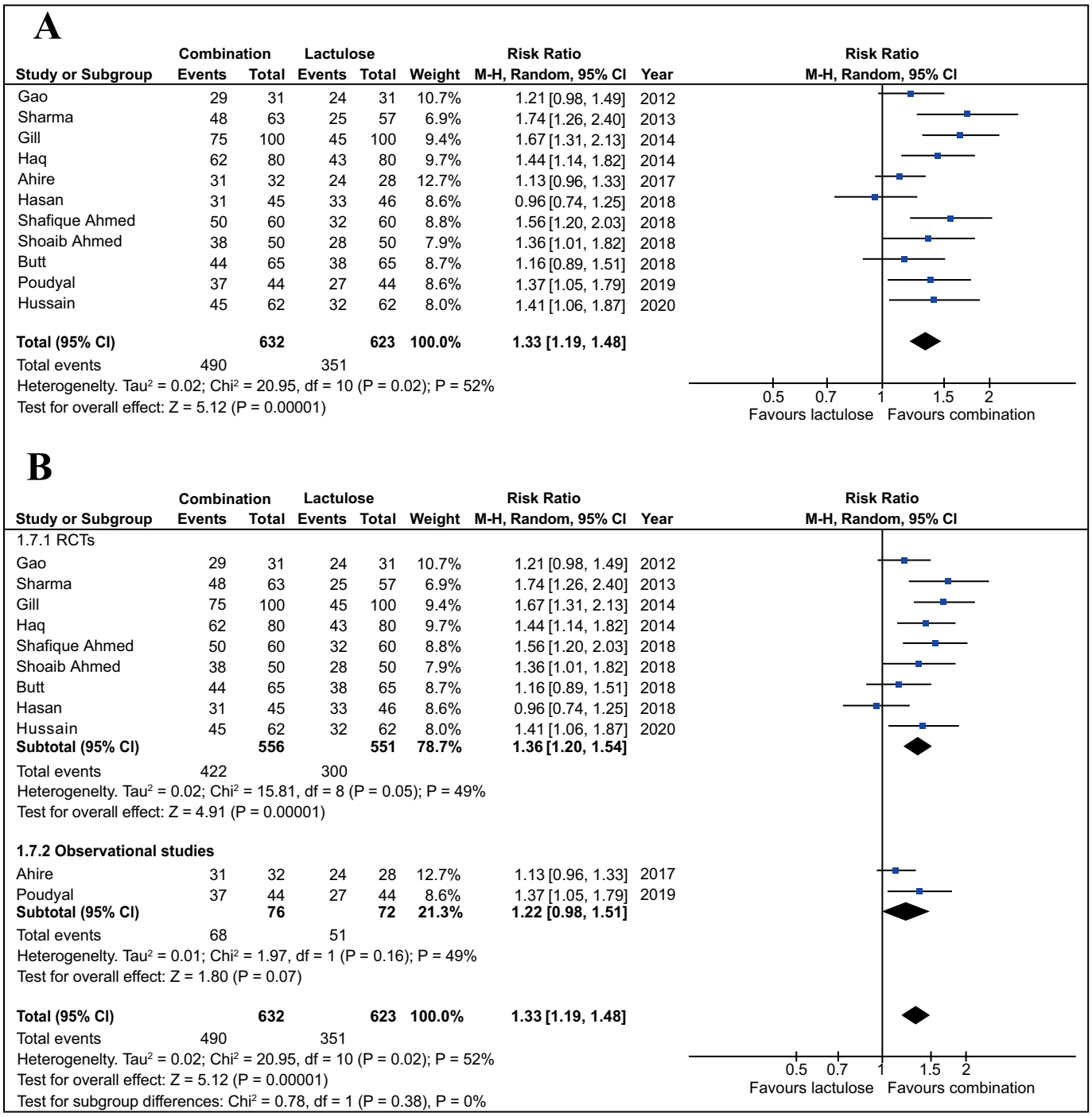


Fig (3): Forest plot for clinical efficacy **(A)** Pooled analysis of all studies, **(B)** Subgroup analysis of Randomized and non-randomized studies.

CI, confidence interval; M-H, Mantel-Haenszel; IV, inverse variance

Among RCT'S the pooled analysis of nine studies [10, 17-19, 23-26] demonstrated a significantly higher clinical efficacy of combination therapy (RR 1.36, 95% CI 1.20 to 1.54, P= < 0.00001, I2=49%) (**Fig. 3**).

Length of Stay

Six studies [17, 18, 20-22, 26] reported the data of hospital stay. The pooled analysis showed no significant association between choice of therapy and length of hospital stay (WMD −1.52, 95% CI −3.22 to 0.18, P=0.08, I2 = 83%) (**Fig. 4**).

HE Recurrence

HE recurrence was reported by four studies only [16, 21, 22, 26] The pooled analysis of these studies showed that there was no significant correlation between treatment groups and the rate of HE recurrence events (RR= 0.61, 95 % CI= 0.35 to 1.05, P= 0.08, I2= 84%) (**Fig. 4**).

Adverse Events

Three out of fifteen studies [9, 16, 17] reported adverse events, and the pooled analysis of these events showed that there was no significant association between the

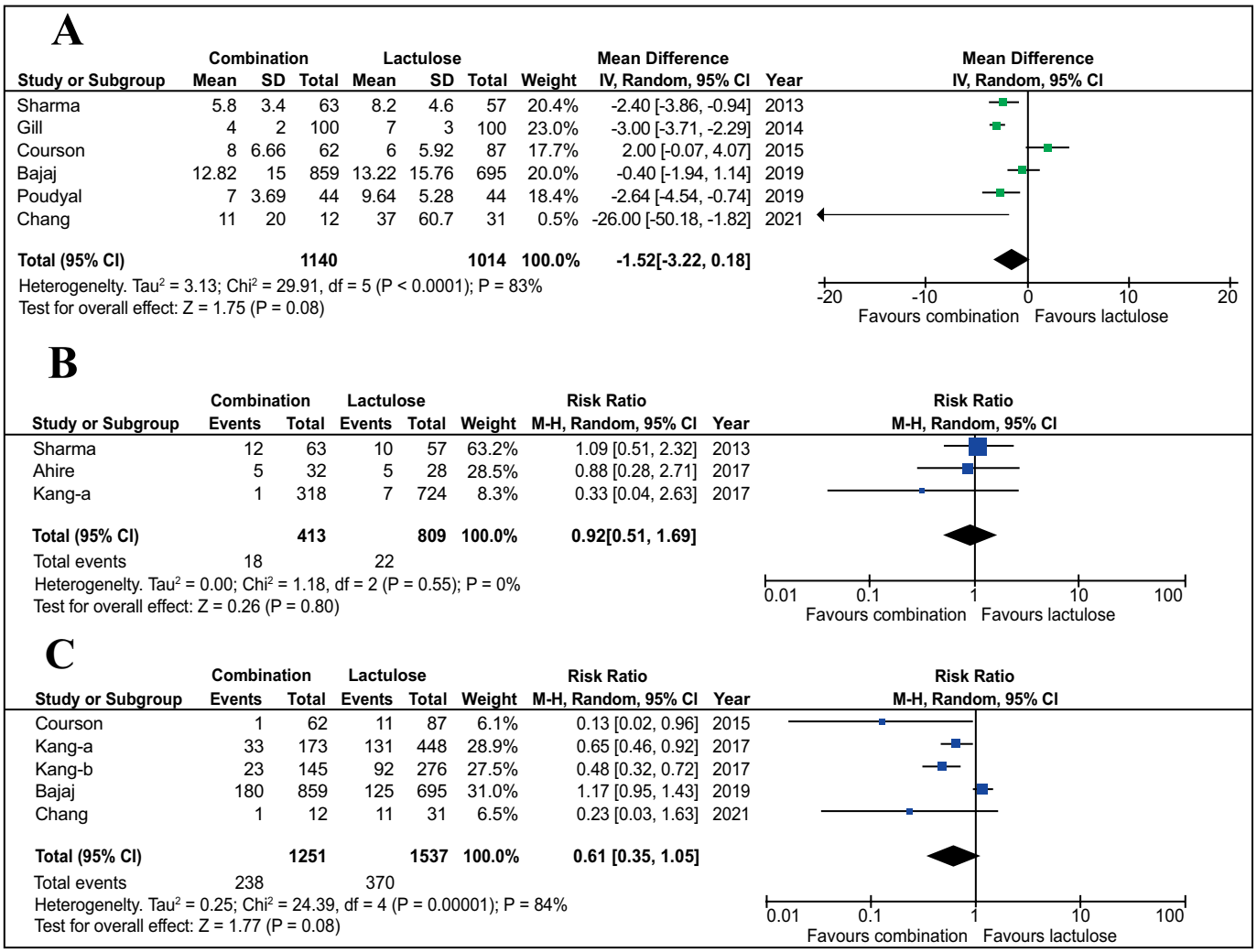


Fig. (4): Forest plots for **(A)** Length of stay, **(B)** Adverse effects, **(C)** HE recurrence.

CI, confidence interval; M-H, Mantel-Haenszel; IV, inverse variance

treatment groups and the risk of adverse events (RR= 0.92, 95% CI= 0.51 to 1.69, P= 0.80, I2 = 0) (**Fig. 4**).

Meta-Regression Analysis

A univariate meta-regression analysis has shown that age had a significant positive correlation with mortality rate (coefficient= 0.022; p<0.001) but an insignificant negative correlation with clinical efficacy (coefficient= -0.012; p=0.112). Moreover, the regression revealed no significant association between gender, mortality, and clinical efficacy. The overall results of meta-regression have shown in Table **2**.

Publication Bias

Publication bias was assessed using funnel plots and Egger's test. No publication bias except for clinical efficacy was identified. (**Supply Appendix A, Table A.3 and Fig. A.1**)

DISCUSSION

Hepatic encephalopathy (HE) is a grave neuropsychiatric consequence of acute or chronic liver failure [28]. The most critical part of managing overt HE is identifying and

Table 2: Univariate regression analysis of mortality and clinical efficacy for mean age and male gender.

Covariate	Outcome	Coefficient	SE	95% CI		p-value
				LL	UL	
Age	Mortality	0.022	0.006	0.011	0.034	< 0.001
	Clinical efficacy	-0.012	0.007	-0.026	0.003	0.112
Gender	Mortality	0.000	< 0.001	-0.000	0.001	0.271
	Clinical efficacy	0.002	0.001	-0.001	0.005	0.147

CI = Confidence interval, LL= lower limit, UL= upper limit.

treating the precipitating factors [29]. Guidelines by the ESAL (European Association for the Study of the Liver) and AASLD (American Association for the Study of Liver Diseases) recommend non- absorbable disaccharide, lactulose, as the first-line agent in managing acute and chronic HE [1]. A meta-analysis of 38 RCTs found that lactulose was superior to placebo in treating and preventing minor and overt HE [30]. Lactulose is a synthetic NAD that reduces ammonia load by its laxative and prebiotic effects with nonserious GI side effects. Other pharmacologic agents such as Branched-chain amino acids (BCAA), Rifaximin, Albumin, L-Ornithine L-Aspartate (LOLA), and Flumazenil have increasingly

been shown to be beneficial in the treatment of HE. Rifaximin is a broad-spectrum antibiotic that acts by modification of gut microbiota's composition and activity and its eubiotic and anti-inflammatory effects [31]. Its benefits in treatment of patients with HE, including reduced blood ammonia levels and improved cognitive performance, have been verified in a network meta-analysis [32]. Our updated meta-analysis, comparing the effectiveness of Rifaximin and lactulose combination therapy with lactulose monotherapy included 15 studies with 4,043 patients as compared to the previous meta-analysis that included 9 studies with 2,276 patients. However, it is worth noting here that the previous meta-analysis included one study with different comparison groups (Rifaximin vs. Rifaximin plus lactulose), which may have biased the results [33].

Our meta-analysis that consisted mainly of patients with overt HE (West Haven Criteria II-IV) demonstrated a relative risk for in-hospital mortality of RR 0.71; 95% CI 0.58–0.88, p=0.002, which shows the combination therapy to significantly reduce mortality as compared to lactulose alone. Similarly, clinical efficacy also improved with combination therapy. However, no significant difference was found in the length of hospital stay, adverse effects, and HE recurrence between both the groups. Similar findings were reported in the previous meta-analysis by Wang *et al.* [11]. In one RCT, the reduction in mortality in the combination group was attributed to a decrease in sepsis-related deaths that could have been due to decreased levels of gut-related endotoxins in the blood [17]. Moreover, despite the similar length of stay with combination therapy, several studies have attested to the fact that addition of rifaximin to the treatment regimen reduces the risk of recurrent hospital admissions [22, 33, 34].

Although no difference (statistically insignificant) was found in adverse events among groups in this analysis, Rifaximin has a safer adverse effect profile due to its gut specificity. Whereas lactulose has been shown to produce mild adverse effects, including nausea and diarrhea [35, 36].

It is shown in the literature that patients with comorbidities such as diabetes mellitus, particularly among male and older patient demographics have a higher prevalence and severity of HE [37]. Based on these findings, our study also explored the effect of sex and age on clinical efficacy and mortality using univariate linear regression model and found no significant correlation except between age and mortality. Furthermore, no significant difference were found in the baseline characteristics of both cohorts except for the fact that most of the studies published in Muslim countries reported infection as a common etiologic agent as opposed to alcoholism commonly reported in non- Muslim countries. Additionally, of the five studies that reported MELD scores, two of them reported a lower score in the combination group [20, 26], while two cohort studies reported a higher MELD score in the lactulose group [21, 22]. A prior history of HE was noted more often in the combination group than the lactulose group [16-22].

This meta-analysis also shows that there is inconsistency between the results of observational studies and RCTs. This might be due to the inherent weaker internal validity of the observational studies. Moreover, the higher heterogeneity of observational studies might be due to the inclusion of large number of older patients and non-randomization.

The progressively increasing healthcare burden of HE is attributed to the frequency of hospital admissions and readmissions, cost per admission and the unappeasable demand of liver transplantation that have only risen than before [38, 39]. While the direct cost of Rifaximin is high as determined in a cost-analysis study by Kang *et al.* [16], it can be argued that the medication's significance in preventing recurrent hospitalizations outweighs any financial risks. Neff *et al.* [33] demonstrated the overall cost, including medication and hospitalization with rifaximin monotherapy, to be 40% less than lactulose. Current guidelines recommend rifaximin as an adjunct in patients with cirrhosis. However, higher-quality trials are needed to determine if combination therapy must be considered as the mainstay of treatment for overt, HE.

LIMITATIONS

Limitations in our study exist with respect to sample size and quality of the included studies. We included both RCTs and non-randomized trials in our analysis to reach a large sample size, which could have potentially led to the introduction of confounding bias. However, subgroup analysis did not reveal any significant alteration in the results. Most trials included in our meta- analysis were of poor quality, one of them being non-blinded, which could have biased the results. Moreover, based on previous meta-analysis by Wang *et al.* we included two additional studies. Full text for both studies are not available online, and the data for these studies was extracted from the previous meta-analysis. Quality of these studies could not be assessed for the same reason. Additionally, clinical efficacy was judged differently in each study on the basis of either HE reversal, HE index improvement, HE recurrence, or readmission rates. Establishment of a proper scale could help in standardized reporting, thereby limiting bias.

CONCLUSION

Despite our study's limitations, we can conclude on the basis of pooled analysis and subgroup RCT analysis that combination therapy is more effective than lactulose monotherapy in terms of reducing mortality and improving clinical efficacy.

SUPPLYMENTERT MATERIAL

Appendix A: Quality assessment of cohort and Randomized control trials using Newcastle Ottawa scale and Cochrane risk of bias tool, Assessment of publication bias using Egger's test and funnel plots.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

All the authors contributed equally to the publication of this article.

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