SYSTEMATIC REVIEW AND META-ANALYSIS

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Comparative Efficacy of Treatment Options for the Prevention of Post-TIPS Hepatic Encephalopathy: A Systematic Review and Network Meta-analysis

Zohaib Ahmed[1], Mona Hassan[2], Syeda Faiza Arif[3], Muhammad Aziz[2], Umair Iqbal[4], Ahmad Nawaz[5], Umer Farooq[6], Wade Lee-Smith[7], Joyce Badal[8], Anas Renno[2], Toseef Javaid[2], Ali Nawras[2], Sammy Saab[9]

1) Dept. of Internal Medicine, University of Toledo, Toledo, Ohio; 2) Division of Gastroenterology and Hepatology, University of Toledo, Toledo, Ohio; 3) University of Toledo Medical Center, Toledo, Ohio; 4) Division of Gastroenterology and Hepatology, Geisinger Medical Center, Danville, Pennsylvania; 5) Division of Internal Medicine, Yale-New Haven Hospital, New Haven, Connecticut; 6) Dept. of Internal Medicine, Loyola Medicine/MacNeal Hospital, Chicago, Illinois; 7) University of Toledo Libraries, University of Toledo, Toledo, Ohio; 8) University of Toledo College of Medicine and Life Sciences, Toledo, Ohio; 9) Dept. of Medicine and Surgery at the David Geffen School of Medicine at UCLA (University of California Los Angeles), Los Angeles, California, USA

Address for correspondence:
Zohaib Ahmed, MD, MPH, CNSC
Department of Internal Medicine, University of Toledo, Toledo, Ohio, USA.
zohaib.ahmed@utoledo.edu

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ABSTRACT

Background & Aims: Transjugular intrahepatic portosystemic shunt (TIPS) is often used in patients with cirrhosis to manage portal hypertension-related complications. Unfortunately, 35-50% of patients develop overt hepatic encephalopathy (HE) after TIPS. However, data on lactulose and rifaximin to prevent post-TIPS HE is limited. Therefore, we aimed to perform a network meta-analysis to investigate the efficacy of multiple pharmacological regimens in the prevention of post-TIPS HE.

Methods: A comprehensive search strategy to identify reports of studies of rifaximin use on post-TIPS hepatic encephalopathy was constructed using truncated keywords, phrases, and subject headings developed in Embase. This strategy was translated to MEDLINE, Cochrane Central Register of Controlled Trials, and the Web of Science Core Collection, with all searches performed on 10 February 2022. No publication date or language limits were used.

Results: The initial search identified 72 studies, and 56 studies were screened after removing duplicates. Five studies, two randomized controlled trials (RCTs) and three retrospective studies, met our inclusion criteria and were included in the final analysis. A total of 840 patients were included, with 65% male. Our meta-analysis did not find a statistically significant difference between lactulose vs placebo/no prophylaxis, nor rifaximin vs placebo/no prophylaxis, nor rifaximin plus lactulose vs placebo/no prophylaxis in the reduction of post-TIPS HE.

Conclusions: Rifaximin alone, lactulose alone, and rifaximin plus lactulose did not significantly reduce the development of post-TIPS HE. Based on the P-scores of the three treatment groups, the combination of rifaximin plus lactulose showed the most promising trend towards preventing post-TIPS HE. More studies, especially large RCTs, are warranted.

Key words: transjugular intrahepatic portosystemic shunt – variceal bleeding – hepatic encephalopathy.

Abbreviations: CI: confidence interval; HE: hepatic encephalopathy; AASLD: American Association for the Study of Liver Diseases; MELD: Model for End-Stage Liver Disease; MINORS: Methodological Index for Non-Randomized Studies; RCT: randomized controlled trial; RR: risk ratio; TIPS: transjugular intrahepatic portosystemic shunt; VB: variceal bleeding.

INTRODUCTION

A transjugular intrahepatic portosystemic shunt (TIPS) is commonly utilized for portal hypertension-related complications such as refractory ascites and secondary prophylaxis of variceal bleeding in cirrhotic patients [1]. However, postprocedural complications following TIPS, especially hepatic encephalopathy (HE), continue to be common and challenging to treat [2].

Hepatic encephalopathy and deteriorating liver function are the most common adverse events after TIPS, and both are linked to a decrease in blood perfusion in the liver due to shunt formation [3]. The introduction of polytetrafluoroethylene-covered stents, which are not linked to an increased risk of HE as compared to bare stents, has dramatically reduced the rate of shunt malfunction [4]. After TIPS, 35-50% of patients experience an episode of overt HE [5]. According to the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL)

guidelines, routine pharmacological prophylaxis of post-TIPS HE is not currently suggested, as evidence for effective prevention is insufficient [6].

The administration of non-absorbable disaccharides and antibiotics, such as lactulose and rifaximin respectively, is often used as secondary prophylaxis for HE in cirrhotic patients [7]. However, data on using lactulose and rifaximin for prevention of post-TIPS HE is limited. Therefore, we conducted a network meta-analysis of the available literature to evaluate the efficacy of different pharmacological regimens in preventing the development of post-TIPS HE.

METHODS

A comprehensive search strategy to identify reports of studies of rifaximin use on post-TIPS hepatic encephalopathy was constructed in Embase (Embase.com, Elsevier) by an experienced health sciences librarian (W.L.S.), using truncated keywords, phrases, and subject headings. This strategy was translated to MEDLINE (PubMed platform, NCBI), Cochrane Central Register of Controlled Trials (CochraneLibrary.com, Wiley), and the Web of Science Core Collection (Web of Science platform, Clarivate) with all searches performed on 10 February 2022 (see Supplementary Information for detailed search strategies). In addition, all results were exported to EndNote 20 citation management software (Clarivate, Philadelphia, PA, USA), and duplicates were removed by successive iterations of EndNote's duplicate detection algorithms and manual inspection.

Inclusion/Exclusion Criteria

We limited our search strategy to include randomized controlled trials (RCTs) and dual-arm cohort studies comparing different interventions and outcomes. We excluded review articles, case reports, studies with 10 or fewer patients, and letters to the editor. The search strategy was not restricted by language or publication date. We included abstracts in our final analysis.

Screening and Data Collection

The studies were screened by two independent reviewers (Z.A. and S.F.A.). The initial screening was based on titles and abstracts, with the full-text screening of relevant publications following. Next, two independent reviewers extracted the data (Z.A. and S.F.A.). Discrepancy in study selection and data extraction was resolved through mutual discussion. Finally, data on demographics (age and gender), indications for TIPS, and outcomes (post-TIPS hepatic encephalopathy) were collected and summarized using Microsoft Excel (Microsoft, Redmond, Washington, United States).

Statistical Analysis

A network meta-analysis using a random-effects model was performed to generate direct and indirect comparisons between treatment groups. The frequentist method was used to rank the interventions, and a P-score was generated. A higher P-score (close to 1.00) corresponded to superior progression-free survival. A p-value of <0.05 was considered statistically significant. A risk ratio (RR) with 95% confidence interval (CI) was calculated. We used ‚R' (Bell Labs, Murray Hill, NJ, USA) to generate our statistical analyses and plots.

RESULTS

The initial search identified 72 studies, and 56 studies were screened after removing duplicates. Five studies, two randomized controlled trials (RCTs) and three retrospective studies, met our inclusion criteria and were included in the final analysis [8-12]. A total of 840 patients were included, with 65% male. The details of study selection are highlighted in the PRISMA flow diagram (Fig. 1). Due to the low number of studies, we did not perform a direct meta-analysis. The most common indication for TIPS was refractory ascites, followed by variceal bleeding. Baseline characteristics, including patient demographics, post-TIPS portosystemic pressure gradient, etiology of liver cirrhosis, and indications for TIPS, are reported in Table I.

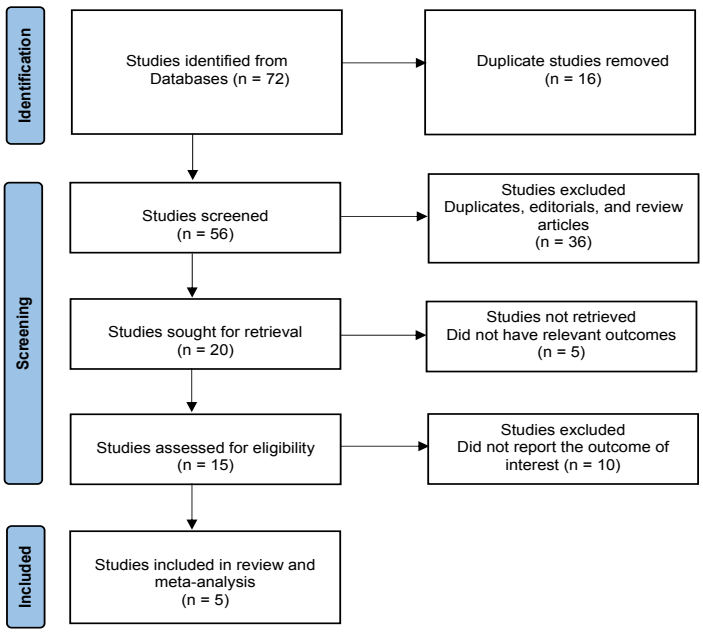

Fig. 1. PRISMA flow diagram of the literature review process.

Table I. Study characteristics

Study (Year, Design)	Demographics (Age, Male)	n, (R /L /RL / Placebo*)	Post-TIPS HE n, [%] (R /L /RL / Placebo*)	Post-TIPS HE, grade	Post-TIPS PSG (mmHg)	Etiology of liver cirrhosis	Indication for TIPS	Previous episodes of HE	Time of treatmen, initiation and dosing	Period of follow up
Bureau et al. (2021, RCT)	Mean age=60 (±8) Male=152 (77%)	186 (93/ -/ -/ 93)	81 (41%) (32 [34%] / - / - / 49 [53%])	Patients=81 Grade I=NR Grade II=59 (73%) Grade III=17 (21%) Grade IV=5 (6%)	Mean=6 (±3)	Alcohol (86%)	Ascites (81%)	Excluded recurrent or persistent overt HE (grade 2 or higher according to West Haven modified criteria); 23/197 (23% had minimal HE at baseline)	2 weeks before TIPS; rifaximin 600 mg BID	168 days
Casadaban et al. (2015, retrospective)	Median age=54 (48-60) Male=114 (60%)	191 (NR)	81 [42%] (NR)	Total HE Episodes= 108 Grade I= 50 (46%) Grade II= 31 (29%) Grade III= 19 (18%) Grade IV= 8 (7%)	Median=7 (5-9)	Alcohol (30%) HBV/HCV (27%) Alcohol and viral (21%)	Variceal bleeding (49%) Refractory ascites/ hepatic hydrothorax (48%)	91/181 (48%) had prior HE: Grade I=28/91 (31%) Grade II=12/91 (13%) Grade III=11/91 (12%) Grade IV=4/91 (4%) Insufficient data to grade 36/91 (40%)	Not standardized (included pre- and post-TIPS treatment); treatment doses not described	30 days
Riggio et al. (2005, RCT)	Mean age=57 (±11) Male=49 (65%)	75 (25/ 25/ -/25)	25 [33%] 8 [32%] / 9 [36%] / - / 8 [32%])	Patients=25 Grade I= NR Grade II= 12 (48%) Grade III= 8 (32%) Grade IV= 5 (20%)	Mean=7 (±2.5)	Alcohol (33%)	Variceal bleeding (67%) Ascites (33%)	11/64 (17%) had prior episodic HE	Immediately after TIPS; lactitol 20 mL TID or rifaximin 400 mg TID	Weekly assessments for 30 days
Seifert et al. (2021, retrospective)	Median age=58 (19-80) Male=142 (61%)	233 (6/ 85/ 59/ 83)	107 [46%] (6 [100%] / 42 [49%] / 16 [27%] / 43 [52%])	Total # Episodes= 127 Grade I= 77 (60.6%) Grade II= 25 (19.7%) Grade III= 18 (14.2%) Grade IV= 7 (5.5%)	Aim <12 during TIPS procedure	Alcohol (52%) Viral (9%) NAFLD (9%)	Ascites (49%) Variceal bleeding (33%)	21% had prior HE: Grade I=38/49 (77.6 %) Grade II=8/49 (16.3%) Grade III=3/49 (6.1%)	Within 72 hours after TIPS; lactulose titrated to 2-3 loose bowel movements or rifaximin 550 mg BID or LOLA 3-6g TID	1, 3, and 12 months
Subramanian et al. (2020, retrospective)	Mean age=57 (±11) Male=88 (61%)	144 (6/ 38/ 73/ 27)	77 [53%] (5 [83%] / 16 [42%] / 47 [64%] / 9 [33%])	NR	NR	HCV (31.1%) Alcohol (60.1%) NASH (23.6%)	- Esophageal variceal bleeding (36%) - Refractory ascites (42%) - Gastric variceal bleeding (19.4%)	17% had a prior episode of HE	NR	12 months

*Placebo or no prophylaxis; RCT: randomized controlled trial; R: rifaximin; L: lactulose or lactitol; RL: both rifaximin and lactulose; LOLA: l-ornithin-l-aspartate; TIPS: transjugular intrahepatic portosystemic shunt; HE: hepatic encephalopathy; PSG: portosystemic pressure gradient; NR: not reported; BID: twice daily; TID: three times daily.

Network Meta-analysis

The network meta-analysis results are summarized in Table II and demonstrated using network forest plots in Fig. 2. Network diagrams for respective forest plots are provided in the supplementary material. Overall, 202 patients received lactulose/lactitol, 138 patients received rifaximin, 137 patients received lactulose plus rifaximin, and 328 patients received placebo/no prophylaxis. There was no significant difference between the lactulose/lactitol versus placebo/no prophylaxis groups (RR=0.84, CI: 0.66-1.06, p=0.15) or between the rifaximin versus placebo/no prophylaxis groups (RR=1.02, CI: 0.82-1.28, p=0.84) in reducing post-TIPS HE. Similarly, the comparison between lactulose plus rifaximin versus placebo/no prophylaxis groups did not achieve statistical significance either (RR=0.86, CI: 0.65-1.13, p=0.27) (Fig. 2). Although the results from these comparisons did not reach statistical significance, the P-score rankings suggest that the combination of lactulose plus rifaximin was the most efficacious intervention with a P-score of 0.73, followed by lactulose/lactitol alone (P-score=0.59), then placebo/no prophylaxis (P-score=0.49), and finally rifaximin alone (P-score=0.19) (Fig. 3).

Table II. Risk of hepatic encephalopathy in the treatment group compared to the placebo/no prophylaxis group

Treatment	RR	CI	p
Lactulose	0.84	0.66 – 1.06	0.15
Rifaximin	1.02	0.82 – 1.28	0.84
Lactulose + Rifaximin	0.86	0.65 – 1.13	0.27

RR: relative risk; CI: confidence interval.

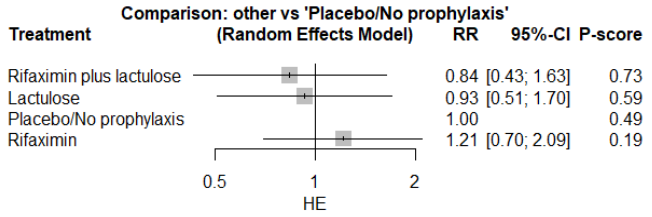

Fig. 2. Network forest plot.

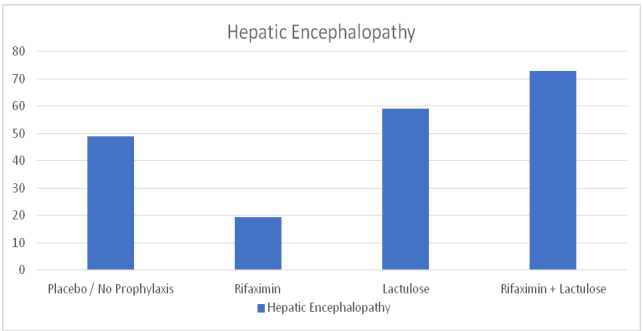

Fig. 3. P-score for each treatment. A higher score demonstrates a lower incidence of hepatic encephalopathy in the intervention group.

Table III. Risk of bias assessment of the included RCTs

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Bureau et al [9]	Low	Low	Low	Low	Low	Low	Low
Riggio et al. [12]	Low	High	High	High	Low	Low	Unclear (no info about blinding)

Bias Assessment

The risk of bias within each study was determined using the Cochrane Risk of Bias tools for RCTs and the Methodological Index for Non-Randomized Studies (MINORS) scale for retrospective cohort studies [13, 14]. Publication bias was assessed qualitatively by visualizing the funnel plot and using Egger's regression analysis quantitatively, although these tools are underpowered with a number of studies below ten. The results from the funnel plot and regression analysis did not reach statistical significance (p=0.9998) (Fig. 5).

DISCUSSION

Our meta-analysis did not find a statistically significant difference between lactulose vs placebo/no prophylaxis, nor rifaximin vs placebo/no prophylaxis in the reduction of post-TIPS HE. There was also no significant difference between the combination of rifaximin plus lactulose vs placebo/no prophylaxis in the prevention of post-TIPS HE, although the combination trended towards highest efficacy based on network ranking using P-scores.

Hepatic encephalopathy continues to be a challenging complication after TIPS placement [15]. Existing evidence on the efficacy of pharmacologic treatment for prevention of post-TIPS HE is conflicting. The RCT by Bureau et al. [9] reported that in patients with cirrhosis who underwent TIPS, rifaximin was well tolerated and significantly reduced the

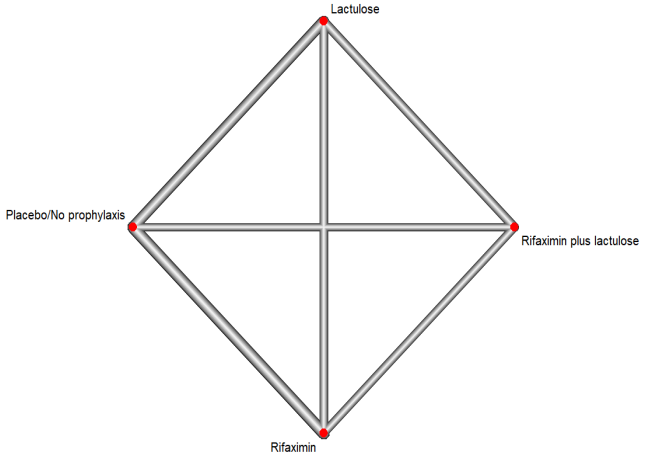

Fig. 4. Network diagram.

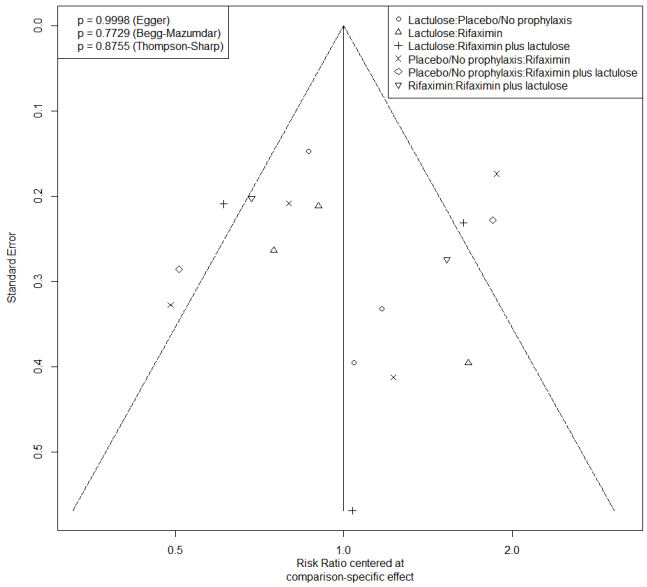

Fig. 5. Funnel plot.

risk for overt HE. An episode of overt HE occurred in 34% of patients in the rifaximin group (n=93) and 53% in the placebo/no prophylaxis group (n=93) during the post-procedural period (odds ratio=0.48, CI: 0.27-0.87) [9]. In contrast, the RCT by Riggio et al. [12] showed that treatment with lactulose or rifaximin is not effective in preventing HE during the first month after TIPS. The one-month cumulative HE incidence observed in each group was similar (p=0.97) [12]. A variety of factors could explain the lack of significant outcomes in the study by Riggio et al. [12]. First, small sample size, and second, rifaximin was prescribed immediately after the TIPS procedure. In contrast, rifaximin was started two weeks before TIPS in the study by Bureau et al. [9]. Thus, it is possible that several days of treatment, regardless of the mode of action, are required before the medication is entirely effective, which potentially could have contributed to the positive outcomes in Bureau et al. [9]. Third, Riggio et al. [12] only followed patients for one month, while Bureau et al. [9] reported cumulative incidence curves for overt HE that showed rifaximin superiority over placebo/no prophylaxis after one month. The retrospective study by Seifert et al. [11] reported lactulose alone had no prophylactic effect; however, the combination of lactulose plus rifaximin decreased HE recurrence at 1, 3 and 12 months after TIPS (p=0.003, p=0.003, p=0.006) [11]. Casadaban et al. [8], in their retrospective study, reported the incidence of post-TIPS HE was not statistically different between lactulose vs. lactulose plus rifaximin groups (p=0.999) [8]. Submaranian et al. [10] also found no significant difference in the incidence of HE in the year after TIPS placement between prophylaxis with rifaximin alone, lactulose alone, or rifaximin plus lactulose when compared to no prophylaxis.

The severity of cirrhosis, the etiology of liver disease, a portosystemic pressure gradient, age, the presence of diabetes, low sodium, prior HE history, and Child-Pugh class have all been linked to HE development after TIPS implantation [16, 17]. Patients with lower serum sodium and a higher Child-Pugh score before TIPS are more likely to suffer from early post-TIPS HE, which is associated with worse long-term survival. In addition, previous studies have shown that hyponatremia can alter brain metabolism and raise the risk of hepatic encephalopathy [18]. These risk factors should be considered before TIPS, as they potentially increase mortality and morbidity. Unfortunately, we were unable to account for these factors in our meta-analysis due to the limited data available.

Due to the lack of evidence of a favorable effect, it is not recommended to regularly use prophylactic treatment to prevent HE following TIPS [19]. Other unsolved questions include the best time to start prophylaxis and how long it should be continued, as current guidelines are vague [20]. PEARL, a prospective multicenter randomized, double-blind, placebo-controlled trial, was recently proposed to assess the impact of HE prevention with lactulose and rifaximin in TIPS patients. According to the protocol, patients will receive lactulose and rifaximin for 72 hours before TIPS implantation and for three months afterwards [21]. Furthermore, in a recent study, Yin et al. [16] developed a nomogram for predicting postoperative HE in cirrhotic patients who received TIPS, which will be a helpful tool for predicting HE before TIPS and risk stratification to guide the therapeutic strategy in patients with cirrhosis [16, 17].

This network meta-analysis has the following strengths: performance of a systematic literature search with well-defined inclusion and exclusion criteria, inclusion of all available comparative studies, and careful exclusion of redundant studies. However, our meta-analysis has several limitations. Firstly, our study is susceptible to selection bias which is inherent to meta-analysis, although every effort was made to conduct a comprehensive review of the literature. Secondly, only a small number of studies, with only two

Table IV. Quality assessment via the Methodological Index for Non-Randomized Studies (MINORS)

Study	Clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow up less than 5%	Prospective calculation of the study size	An adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analyses	Total Score
Casadaban et al. [8]	2	2	1	2	0	2	2	0	0	0	0	0	11
Seifert et al. [11]	2	2	1	2	0	2	2	0	2	2	1	2	18
Subramanian et al. [10]	2	2	1	2	0	2	0	0	2	2	0	1	14

RCTs, were found in the available literature and included in the final meta-analysis. The small number of patients in each intervention arm increase the likelihood of error. Thirdly, three studies were retrospective observational studies which are susceptible to a high risk of publication bias and selectivity reporting. Additionally, our publication bias assessment tools are underpowered with less than ten studies. Fourthly, many patients had baseline HE or a history of HE of varying West Haven grade before TIPS (Table I), which may have affected the study results. Fifthly, heterogeneity concerning time of treatment initiation, medication dosing, and follow-up period between the trials may also have influenced our results. Finally, the mix of RCTs and retrospective studies, as well as the heterogeneity of study methodologies and baseline HE, might violate the transitivity assumption required for network meta-analysis. Despite its limitations, this network meta-analysis is the first to summarize the available literature on several strategies to prevent post-TIPS HE.

CONCLUSIONS

Rifaximin alone, lactulose alone, and rifaximin plus lactulose did not significantly reduce the development of post-TIPS HE. Based on the P-scores of the three treatment groups, the combination of rifaximin plus lactulose showed the most promising trend towards preventing post-TIPS HE, although further investigation is required. Additional studies, particularly large RCTs, are also warranted to determine the ideal time to start the regimen and duration of treatment.

Conflicts of interest: S.S. served as a speaker for Salix, the rifaximin manufacturer. The rest of the authors declare no conflict of interests.

Authors' contribution: Z.A. conceived the study, collected and interpreted data, drafted the manuscript and revised the study. S.F.A. and J.B. collected data and drafted the manuscript. M.A. performed the statistical analyses and manuscript revisions. U.I. revised the manuscript. W.L.S. conceived the study search strategy, collected data, and drafted the manuscript. A.R. revised the manuscript. A.N., M.H. and S.S. conceived the study and revised the manuscript critically.

Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://dx.doi.org/10.15403/jgld-4508

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