SYSTEMATIC REVIEW AND META-ANALYSIS

DOI: http://dx.doi.org/10.15403/jgld-182

Efficacy of Probiotics and Prebiotics in Prevention of Infectious Complications Following Hepatic Resections: Systematic Review and Meta-Analysis

Yu Gan, Song Su, Bo Li, Chen Fang

Department of Hepato-biliary Surgery, Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, China

Address for correspondence:
Yu Gan
Department of Hepato-Biliary Surgery, Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan,China,
gygxylyfy@163.com

Received: 20.03.2019
Accepted: 27.05.2019

ABSTRACT

Background & Aims: Infections occurring after hepatic resection cause significant morbidity, mortality, and prolonged hospitalization. Probiotics and prebiotics are considered to offer protection against post-operative infections. We aimed to determine the effect of probiotics and prebiotics on the post-operative infection rate after hepatic resection by conducting a systematic review and a meta-analysis.
Method: We searched various databases, namely, the PubMed, Medline, Embase, and Cochrane Controlled Trials Registry (CENTRAL), for randomized controlled trials evaluating the effect of probiotics and/or prebiotics on the infection rate following hepatic resection. Extracted data were pooled and subsequently used in a meta-analysis with a random-effects model. Review was reported following the PRISMA guidelines.
Results: A total of 4 studies comprising 205 patients were included for our meta-analysis. The infection rates in the probiotic group and placebo group were 11.7% and 30.3%, respectively (p<0.001). The pooled risk ratio (RR) was 0.41 (95% confidence interval [CI]: 0.128–0.730). Subgroup analysis indicated that the wound infection rate in the probiotic group (5.3%) was significantly lower than that in the placebo group (RR: 0.387, 95% CI: 0.155–0.970, p=0.043). Furthermore, probiotics/prebiotics decreased the duration of hospital stay (-0.57 days; 95% CI: -0.861 to -0.274; p<0.001) and antibiotic use (mean difference: -3.89 days, 95% CI: -4.17 to -3.60; p<0.001). There was no significant statistical heterogeneity.
Conclusion: Our findings show that administration of probiotics and/or prebiotics prior to operation day decreases the infection rate post-liver resection and could shorten the duration of hospitalization and antibiotics use.

Key words: probiotics – post-resection – hepatic resection – meta-analysis.

Abbreviations: ICU: intensive care unit; RCTs: randomized controlled trials.

INTRODUCTION

Hepatic resection is an important step in the treatment of several types of malignant hepatic neoplasms [1, 2]. In patients who can tolerate the procedure, hepatectomy improves the chances of achieving complete remission of both primary and secondary cancers [3–5]. Hepatectomy for hepatic malignancies has become increasingly common in recent years, and in experienced hands, the procedure has been reported to significantly improve the outcomes [6–17]. Despite the significant benefits of the procedure, the overall mortality rate associated with the procedure remains high, at about 3.5% [18]. Post-operative morbidity necessitating prolonged hospital stay after hepatic resection is also high at 10%–15% [18]. Moreover, infectious complications represent an independent risk factor of postoperative morbidity and mortality and are observed in 12% to 23% of patients experiencing hepatic resection, including respiratory infections, intra-abdominal infection, and wound infections [19, 20]. Postoperative infectious complications are particularly important as they decrease long-term survival [20].

Probiotics and prebiotics have been identified as protective agents against post-operative infections. The pre-surgical administration of antibiotics and the surgical trauma together cause imbalance of gut microbiome and intestinal epithelial barrier dysfunction, thereby triggering the translocation of enteric bacteria to the mesenteric lymph nodes [21]. Probiotics and prebiotics are believed to stabilize the intestinal barrier by preventing bacterial translocation, thus protecting against infections. Indeed, probiotics can affect the intestinal ecosystem by stimulating the mucosal immune and non-immune mechanisms through antagonism competition with potential pathogens [22, 23]. Probiotics also decrease the infection rate by suppressing pathogenic microorganisms [22].

Some studies have revealed that probiotics may decrease the rate of postoperative infection and thereby decrease the duration of hospital stay. However, the current guidelines offered by the European Association for Study of the Liver (EASL) and the American Association for the Study of Liver Disease (AASLD) do not include probiotics as part of the therapeutic protocol for hepatic resection. We performed this meta-analysis to elucidate the effect of probiotic/prebiotic administration on the rate of operative morbidity and mortality, as well as their effect on hospitalization period.

METHODS

Search strategy and study selection

We searched various databases, including PubMed, Medline, Embase, and Cochrane Controlled Trials Registry (CENTRAL), by using the search terms: “hepatic resection” OR “hepatectomy” OR “surgical resection AND liver” AND “probiotics” OR “prebiotics” OR “synbiotics”. No restrictions were placed on language or date of publication. Additionally, we checked the references cited in the selected reviews and also contacted researchers who are experts in this field to ensure that the search was truly comprehensive. The inclusion criteria in this study were as follows: (1) randomized, placebo-controlled trials (RCTs) that involved an experimental or intervention arm and a control arm, both of which differed only in terms of whether or not a probiotic or prebiotic was administered and (2) reporting of the risk of liver resection in each arm.

Outcome assessment

The primary outcome evaluated in this study was the effect of probiotics on the rate of infections. The secondary outcomes were duration of hospital stay and intensive care unit (ICU) stay, and antibiotic administration as well as 30-day mortality. Bacteremia was diagnosed when blood culture was positive for bacterial growth. The following definitions of infections were used in this study: (a) wound infection was defined by the presence of purulent discharge appearing spontaneously or on surgical expression, with a positive culture study; (b) intra-abdominal infection was defined as purulent discharge collected from the abdomen that tested positive for bacterial growth on culture or as fluid collection requiring a drainage procedure.

Data extraction

Two investigators (Y.G. and S.S.) independently examined the abstracts of the extracted papers and selected those suitable for review. Discrepancies in their opinions were resolved by consulting another reviewer (B.L.). The key characteristics of each selected study were summarized, including the year of publication, country of study, study design, patient characteristics (age and gender), usage of probiotics and/or prebiotics, rate and type of postoperative infection, duration of hospital stay, ICU stay, and antibiotic duration and 30-day mortality rate. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [24], guidelines were applied in this meta-analysis.

Assessment of study quality

Each study was independently evaluated for quality by each of the investigators.

The risk of bias in RCTs was assessed using a modified version of the Cochrane Collaboration’s tool for assessing risk of bias [25]. Each trial was scored as high, low, or unclear risk of bias on the basis of the following aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome and assessment, incomplete outcome data, selective reporting, and other bias.

Statistical methods

To evaluate the differences in rate of infection between the intervention and the control groups, dichotomous data were analyzed using a risk ratio (RR) with 95% confidence intervals (CI). Chi-square and I^2 tests were all performed to judge the heterogeneity of clinical trial results and decided the analysis model (fixed-effect model or random-effect model). The selection of fixed-effects model or random-effects model depended on the size of the heterogeneity among the included studies. The continuous variables were expressed as the mean±standard deviation (SD) and analyzed by mean difference (MD). Subgroup analyses were performed to assess any significant heterogeneity between subgroups (I^2>50% or p <0.10). Sensitivity analyses were performed to examine the effect of excluding lower quality studies Publication bias was assessed by using the funnel plot with the bias indicator test from the Egger test. Statistical analyses were performed with Stata version 12 (Stata Corporation, College Station, TX, USA) and Review Manager, version 5.3 (Nordic Cochrane Centre, Oxford, England), with a 2-tailed p values of <0.05 being considered significant.

RESULTS

Search results

Our database search retrieved 127 unique references of which 123 were excluded on the basis of the above mentioned inclusion criteria. The four remaining RCTs [26-29] that satisfied the inclusion criteria were included in the meta-analysis; these studies together included a total of 205 participants (103 treated with probiotics/prebiotics and 102 controls) (Fig. 1). Three of these studies were from Japan, while the remaining one was from Germany (Table I). In the patient cohort, male patients were more than females (144 males), with the mean age of 62 years.

The type and quantity of the probiotics administered were different. In their respective intervention groups, all studies used fiber-rich and enteral nutrition in addition to the administration of probiotics and prebiotics, either alone or in combination (called synbiotics). In all the studies, the patients received antibiotic prophylaxis as a single intravenous drip infusion 30 minutes before surgery. Probiotic group received probiotics on the day of surgery in three trials [26, 28, 29]

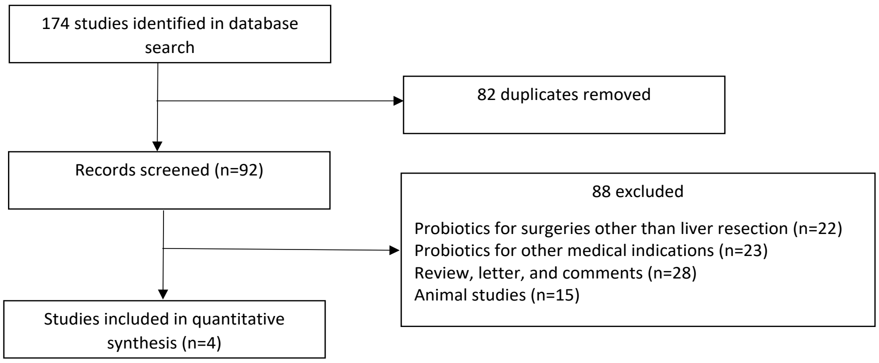

Fig. 1. PRISMA flow diagram of the systematic article selection process.

and on the day before operation in one [27]. The endpoints examined were the overall rate of postoperative infection, type of postoperative infection, duration of ICU stay and hospital stay, adverse effects and 30-day mortality.

Risk of bias

We performed the risk of bias table based on the Cochrane Handbook for Systematic Review of Interventions (Fig. 2). All RCTs reported a clear inclusion and exclusion criteria and suggest a methodology of randomization, using a randomization sequence generated by computer. Among them, one RCT [29] showed that allocation concealment was achieved by a sealed envelope and demonstrated double blinding. We found a low risk of bias regarding incomplete outcome data or selective outcome reporting. Judgments regarding each risk of bias item were presented as percentages across all the included studies in Fig. 3.

Meta-analysis

Rate and type of postoperative infections

The present study included four RCTs and was designed to investigate the effect of probiotics on the incidence of infections. The infection rate in the probiotics group was 11.7%, whereas

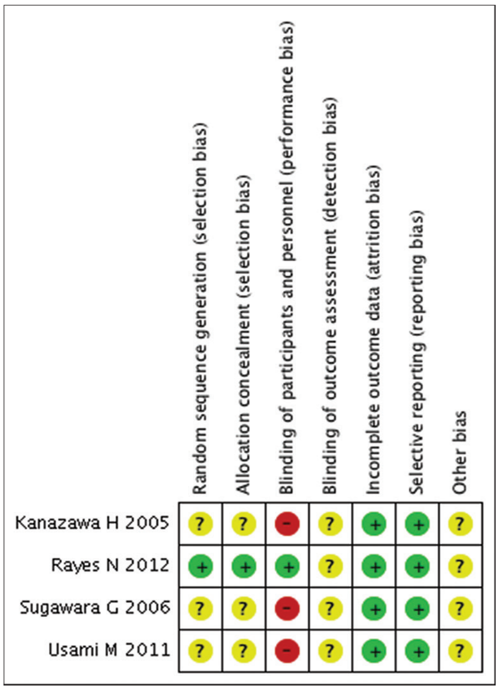

Fig. 2. Risk of bias graph: review of authors' judgements regarding each risk of bias item presented as percentages across all included studies.

Table I. Studies' characteristics.

Study	Country	No of patient		Male		Study design	Probiotics used	Control used	Time probiotic started
		Probiotic Group	Control Group	Probiotic Group	Control Group				
Sugawara et al. [26]	Japan	41	40	23	23	Prospective RCT	Enteric nutrition + fibers + probiotic:80 mL bottle of Yakult 400.100-mL bottle of Bifiel	Enteric nutrition + fibers	On the day of operation and continued 14 days after
Kanazawa et al. [27]	Japan	21	23	15	14	Prospective RCT	Enteric nutrition + fibers +probiotic:. Yakult BL Seichōyaku	Enteric nutrition+ fibers	On the day of operation and continued 14 days after
Usami et al. [28]	Japan	32	29	29	26	Prospective RCT	Enteric nutrition + fibers + probiotic:. Yakult BL Seichōyaku	Enteric nutrition+ fibers	On the day of operation and continued 14 days after
Rayes et al. [29]	Germany	9	10	8	6	Prospective RCT	Enteric nutrition + fibers + probiotic:. Synbiotic 2000	Enteric nutrition + fibers	On the day of operation and continued 10 days after

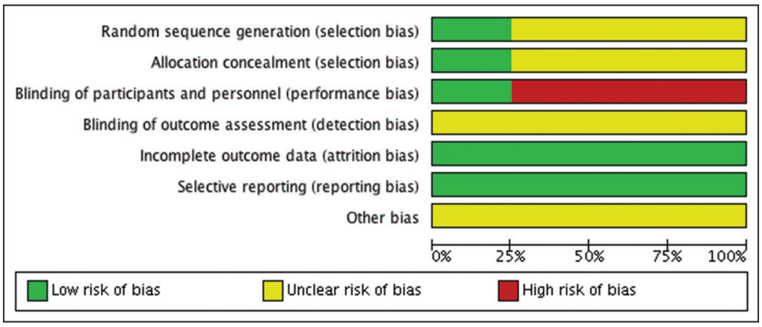

Fig. 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

that in the control group was 30.3% (RR: 0.41, 95% CI: 0.23–0.730; p <0.001), with low heterogeneity (I^2: 32,4%) (Fig. 4). In the control arm, wound infection was the most common cause of infection (15.2%), followed by intra-abdominal infection (14.1%). However, in the intervention group, the majority of infections were intra-abdominal (6.3%). A subgroup analysis of the infection types showed a significant decrease in the rate of wound infection in the intervention group (5.3%), as compared to the rate in the control group (15.2%) (RR: 0.387, 95% CI: 0.155–0.970, p=0.043), without statistical heterogeneity (I^2: 0%) (Fig. 5) No significant benefit of the administration of probiotics was noted on the rate of intra-abdominal infection (RR: 0.482, 95% CI: 0.2–1.163; p=0.104), without statistical heterogeneity (I^2: 0%) (Fig. 6).

Duration of hospital stay and intensive care unit stay

The use of probiotics/prebiotics significantly decreased the duration of hospital stay, with a mean difference (MD) of -0.57 days (95% CI: -0.861, -0.274; p<0.001) (Fig. 7), without statistical heterogeneity (I^2: 0%). However, no significant difference was noted in the duration of the ICU stay between the intervention group and control group (MD: -0.061 days, 95% CI: -0.322 to -0.444; P=0.754; I^2=0%) (Fig. 8).

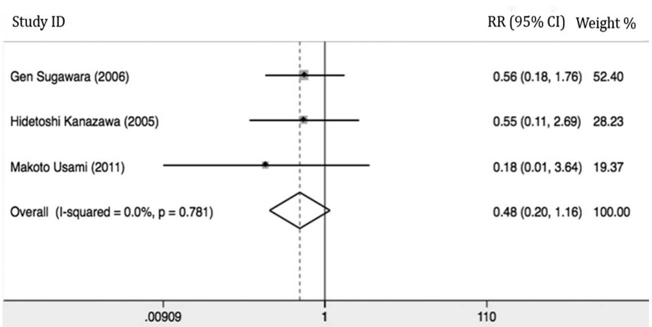

Fig. 6. Relative risk of intra-abdominal infection rate.

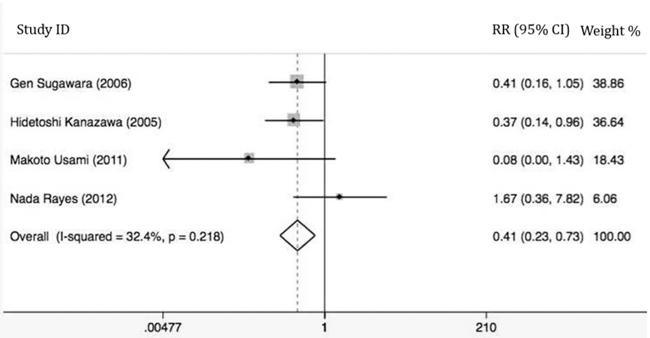

Fig. 4. Relative risk of overall infection rate.

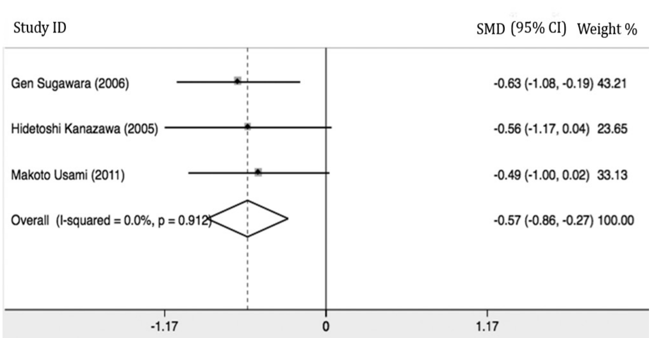

Fig. 7. Difference in median duration of hospital stay in days.

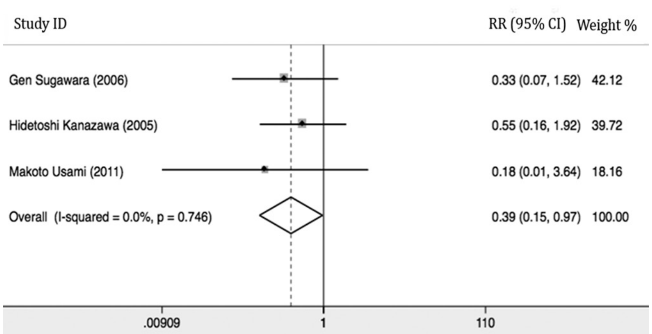

Fig. 5. Relative risk of wound infection rate.

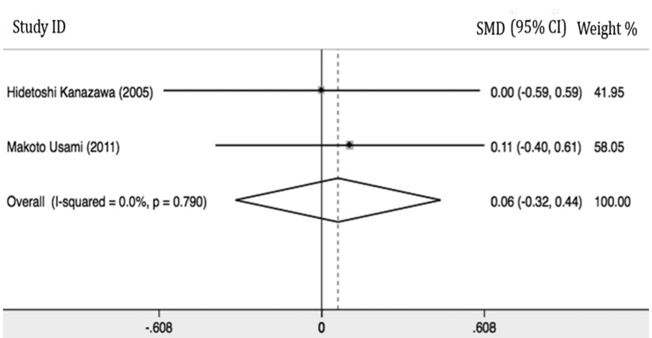

Fig. 8. Difference in median duration of ICU stay in days.

Duration of antibiotic use

The use of probiotics or prebiotics also shortened the duration of antibiotic use (MD= -0.460, 95% CI: -0.816, -0.105; p=0.11), (I^2: 0%) (Fig. 9).

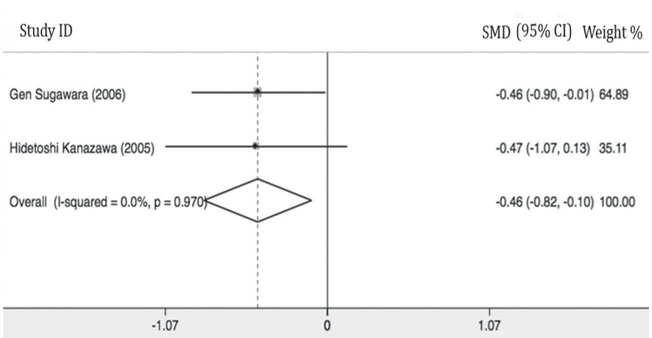

Fig. 9. Difference in median duration of antibiotic use in days.

Thirty-day mortality

None of the studies had recorded any mortality occurring during the study period.

Sensitivity analysis

We also performed a sensitivity analysis whereby each study was eliminated from the analysis, one at a time. The results of the sensitivity analyses showed that there was no change in the direction or the statistical significance of the RRs or MDs obtained for any of the parameters considered or the level of heterogeneity in the analyses or subgroup analyses.

Publication bias

Publication bias was assessed by a funnel plot diagram. The funnel plot diagram of postoperative postoperative infections was symmetrical and did not indicate the existence of publication bias with the Egger test (p=0.716) (Fig. 10). However, this assessment cannot prove the absence of bias due to the small number of studies.

DISCUSSION

Hepatic resection involves the removal of a part of the liver, mainly for cancer or pre-cancerous growths. This procedure

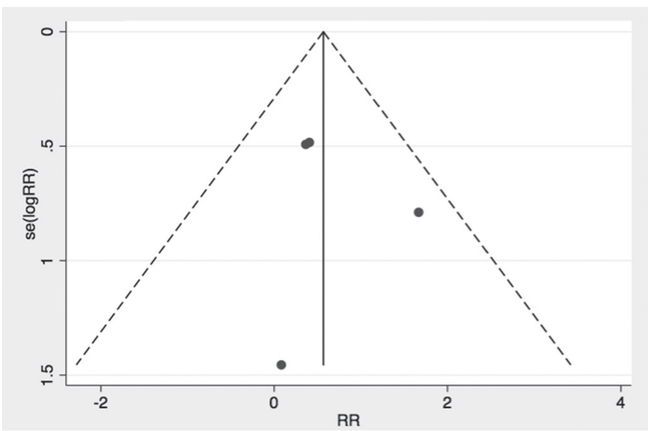

Fig. 10. Funnel plot showing no publication bias.

is a major surgery, and the risk of mortality and postoperative complications associated with this procedure is 3.5% and 10–15%, respectively (defined as complications resulting from prolonged hospital stay). Various proposals have been put forth for achieving a decrease in the rate of postoperative infectious complications after hepatic resection.

Our meta-analysis contained four RCTs with 205 participants. In all the four studies, both groups received enteral treatment within the first 24 hours of the operation, while the probiotic group received extra probiotics. This beneficial effect of probiotics may reduce infectious complications after surgery, especially high-risk hepatectomy [15, 27]. Our results strongly suggest that probiotics reduce postoperative infections.

Our results also showed that patients who received enteral nutrition and probiotics required a shorter duration of hospital stay and antibiotics administration than those who received enteral nutrition only, decreasing the overall cost, without causing any additional adverse effects. All studies provided data on mortality; the pooled analysis showed no significant differences between the two strategies. This may be attributed to the small number of studies included in this study.

A previous Cochrane review [30] evaluating different therapeutic agents showed that antibiotics, prebiotics and probiotics were able to prevent and manage infection complications after liver operation. This Cochrane review included two RCTs that compared the combination of prebiotics and probiotics to the use of enteral nutrition only [26, 27]. Similar to our meta-analysis, this review revealed that there was no difference between the two regimens in terms of mortality. However, contrary to our findings, their study did not show significant effect on the rate of bacterial infection or length of ICU stay or hospital stay. Their study did not provide any subgroup analysis on the infection types. The Cochrane review could not include the studies by Usami et al. [28] and Rayes et al. [29], which were published later. We believe that the differences between our findings and theirs may be attributed to the differences in the nature of the included studies.

Our meta-analysis has some limitations. Firstly the methodological quality of the trials included in the meta-analysis has important problems. Only one study had clear allocation concealment, and was double blinded. This high quality study could not show a difference between infections. The other three studies, although randomized, had no clear randomization technique, the allocation concealment was not clear, and they were not double blinded. Thus three sources of bias question their internal validity, especially the allocation concealment for selection bias, and the blinding for performance and detection biases. These lower quality studies showed a tendency for lower infections, the main outcome of interest in this meta-analysis.

Secondly, different brand, concentrations and usage of probiotics were recommended in this study, which may produce bias in this research. Three of the four included trials had chosen Yakult BL Seichōyaku (Yakult Honsha, Tokyo, Japan) as probiotics [26-28]. Another study [29], however, chose Synbiotic 2000R (Medipharm, Kågeröd, Sweden and Des Moines, Iowa, USA) as probiotics. Thirdly, our meta-analysis included four studies, but three of them were performed in the same country, which limits the generalizability of the findings to some extent; nevertheless, the patient populations in the three studies differed widely. Additional studies across various ethnicities would help clarify whether race influences the extent of benefit obtained from the use of probiotics and/ or prebiotics. Fourthly, only four RCTs were included, with the sample size in each trial being small in number.

CONCLUSION

Our findings show that administration of probiotics and/ or prebiotics prior to operation day decreases the post-liver resection infection rate and could shorten the duration of hospitalization and antibiotics use. The meta-analysis included 4 RCTs, but only one with high quality. As the evidence quality is low, further research is required.

Conflict of interest: None to declare.

Authors' contributions: Y.G. and S.S.: data acquisition and analysis; Y.G. and C.F.: statistical analysis. Y.G: drafted the article; Y.G. and B.L. study design; B.L.: critical revision and final approval.

Acknowledgments: We thank Department of Hepato-Biliary Surgery, The Affiliated Hospital of Southwest Medical University for providing study data.

REFERENCES

1. Benson AB 3rd, D'Angelica MI, Abbott DE, et al. NCCN Guidelines Insights: Hepatobiliary Cancers, Version 1.2017. J Natl Compr Canc Netw 2017;15:563-573.
2. Vitale A, Peck-Radosavljevic M, Giannini EG, et al. Personalized treatment of patients with very early hepatocellular carcinoma. J Hepatol 2017;66:412-423. doi:10.1016/j.jhep.2016.09.012
3. Hyun MH, Lee YS, Kim JH, et al. Hepatic resection compared to chemoembolization in intermediate to advanced stage hepatocellular carcinoma: A meta-analysis of high-quality studie. Hepatology 2018;68:977-993. doi:10.1002/hep.29883
4. Park EK, Kim HJ, Kim CY, et al. A comparison between surgical resection and radiofrequency ablation in the treatment of hepatocellular carcinoma. Ann Surg Treat Res 2014;87:72–80. doi:10.4174/astr.2014.87.2.72
5. Roayaie S, Jibara G,Tabrizian P, et al. The role of hepatic resection in the treatment of hepatocellular cancer. Hepatology 2015;62:440-451. doi:10.1002/hep.27745
6. Chua DW, Xin KY, Xin LY, et al. Pre-operative predictors of early recurrence/mortality including the role of inflammatory indices in patients undergoing partial hepatectomy for spontaneously ruptured hepatocellular carcinoma. J Surg Oncol 2018;118:1227-1236. doi:10.1002/jso.25281
7. Yasuda S, Nomi T, Hokuto D, Yoshikawa T, Matsuo Y, Sho M. Liver Regeneration After Major Liver Resection for Hepatocellular Carcinoma in the Elderly. J Invest Surg 2018 Nov 2:1-7. doi:10.1080/08941939.2018.1517839
8. Kokudo T, Hasegawa K, Matsuyama Y, et al. Liver resection for hepatocellular carcinoma associated with hepatic vein invasion: A Japanese nationwide survey. Hepatology 2017;66:510-517. doi:10.1002/hep.29225
9. Mokdad AA, Singal AG, Yopp AC. Treatment of Liver Cancer. JAMA 2016;315:100. doi:10.1001/jama.2015.15431
10. Lim C, Osseis M, Lahat E, et al. Safety of laparoscopic hepatectomy in patients with hepatocellular carcinoma and portal hypertension: interim analysis of an open prospective study. Surg Endosc 2019;33:811-820. doi:10.1007/s00464-018-6347-1
11. Koh YX, Tan HL, Lye WK, et al. Systematic review of the outcomes of surgical resection for intermediate and advanced Barcelona Clinic Liver Cancer stage hepatocellular carcinoma: A critical appraisal of the evidence. World J Hepatol 2018;10:433-447. doi:10.4254/wjh.v10.i6.433
12. Zhou Y, Wu L, Xu D, Wan T, Si X. A pooled analysis of combined liver and inferior vena cava resection for hepatic malignancy. HPB (Oxford) 2017;19:768-774. doi:10.1016/j.hpb.2017.05.008
13. Su TS, Liang P, Liang J, et al. Long-Term Survival Analysis of Stereotactic Ablative Radiotherapy Versus Liver Resection for Small hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 2017;98:639-646. doi:10.1016/j.ijrobp.2017.02.095
14. Ryu T, Takami Y, WadaY, et al. Double- and Triple-Positive Tumor Markers Predict Early Recurrence and Poor Survival in Patients with hepatocellular carcinoma within the Milan Criteria and Child-Pugh Class A. J Gastrointest Surg 2017;21:957-966. doi:10.1007/s11605-017-3394-1
15. Wang K, Eguchi S, Hidaka M, et al. Comparison of the outcomes of hepatocellular carcinoma after hepatectomy between two regional medical centers in China and Japan. Asian J Surg 2017;40:380-388. doi:10.1016/j.asjsur.2016.03.002
16. Lim C, Compagnon P, Sebagh M, et al. Hepatectomy for hepatocellular carcinoma larger than 10 cm: preoperative risk stratification to prevent futile surgery. HPB (Oxford) 2015;17:611-623. doi:10.1111/hpb.12416
17. Yamashita Y, Tsuijita E, Takeishi K, et al. Trends in surgical results of hepatic resection for hepatocellular carcinoma: 1,000 consecutive cases over 20 years in a single institution. Am J Surg 2014;207:890–896. doi:10.1016/j.amjsurg.2013.07.028
18. Xourafas D, Pawlik TM, Cloyd JM. Early Morbidity and Mortality after Minimally Invasive Liver Resection for Hepatocellular Carcinoma: a Propensity-Score Matched Comparison with Open Resection. J Gastrointest Surg 2018 Oct 30. doi:10.1007/s11605-018-4016-2
19. Wu CC, Yeh DC, Lin MC, Liu TJ, P'eng FK. Prospective randomized trial of systemic antibiotics in patients undergoing liver resection. Br J Surg 1998;85:489-493.
20. Takahashi Y, Takesue Y, Fujiwara M, et al. Risk factors for surgical site infection after major hepatobiliary and pancreatic surgery. J Infect Chemother 2018;24:739-743. doi:10.1016/j.jiac.2018.05.007
21. Nastos C, Kalimeris K, Papoutsidakis N, et al. Bioartificial liver attenuates intestinal mucosa injury and gut barrier dysfunction after major hepatectomy: Study in a porcine model. Surgery 2016;159:1501-1510. doi:10.1016/j.surg.2015.12.018
22. Gunduz M, Murakami D, Gunduz I, et al. Recurrent bacterial translocation from gut and sepsis in Head and neck cancer patients and its prevention by **probiotics**. Med Hypotheses 2018;120:124-127. doi:10.1016/j.mehy.2018.08.020
23. Zhang Y, Chen J, Wu J, Chalson H, Merigan L, Mitchell A. Probiotic use in preventing postoperative infection in liver transplant patients. Hepatobiliary Surg Nutr 2013;2:142-147. doi:10.3978/j.issn.2304-3881.2013.06.05
24. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 2009;62:e1-e34. doi:10.1016/j.jclinepi.2009.06.006

25. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928. doi:10.1136/bmj.d5928
26. Sugawara G, Nagino M, Nishio H, et al. Perioperative symbiotic treatment to prevent postoperative infectious complications in biliary cancer surgery: A randomized controlled trial. Ann Surg 2006;244:706–714. doi:10.1097/01.sla.0000219039.20924.88
27. Kanazawa H, Nagino M, Kamiya S, et al. Synbiotics reduce postoperative infectious complications: A randomized controlled trial in biliary cancer patients undergoing hepatectomy. Langenbeck's Archives of Surgery 2005;390:104–113. doi:10.1007/s00423-004-0536-1
28. Usami M, Miyoshi M, Kanbara Y, et al. Effects of perioperative synbiotic treatment on infectious complications, intestinal integrity, and fecal flora and organic acids in hepatic surgery with or without cirrhosis. JPEN J Parenter Enteral Nutr 2011;35:317-328. doi:10.1177/0148607110379813
29. Rayes N, Pilarski T, Stockmann M, Bengmark S, Neuhaus P, Seehofer D. Effect of pre- and probiotics on liver regeneration after resection - a randomised, double-blind pilot study. Benef Microbes 2012;3:237-244. doi:10.3920/BM2012.0006
30. Gurusamy KS, Naik P, Davidson BR. Methods of decreasing infection to improve outcomes after liver resections. Cochrane Database Syst Rev 2011;(11):CD006933. doi:10.1002/14651858.CD006933.pub2