

Re: Revision for “Relationship of non-alcoholic fatty liver disease to colorectal adenomatous and hyperplastic polyps” (**ESPS Manuscript NO: 34420**)

Dear Editors,

We thank you and the reviewers for giving us the opportunity to revise our manuscript.

We have carefully studied the comments raised by the reviewers and editors, and revised the paper accordingly. The following are point-by-point responses to the editors’ and reviewers’ comments. All the modifications have been highlighted in yellow in the revised manuscript.

Should you have any questions, please contact us without any hesitation.

We look forward to your favorable decision.

Yours truly,

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Reviewer #1

Reviewer's code: 00058403

COMMENTS TO AUTHORS

This is a retrospective study with large sample loss. The p values are not shown in Tables 1 and 2. There is no identification of how confounding variables were selected, why not BMI?

Response

Thank you very much for reviewing and your comments. The p values have been added into Table 1 and Table 2 in accordance to your advice. In this study, model C consisted of all potential confounding factors to validate that NAFLD is an independent risk factor for colorectal adenomatous and hyperplastic polyps. All covariates included in the model C meet the criteria for confounders and have possibility to affect the outcome. For this study, adjustment was made to control for NAFLD, gender, age, smoking, alcohol and MS. Health-related behaviors are represented by smoking, alcohol consumption, while metabolic risk factor are represented by MS that including hyperlipemia, glucose intolerance, hypertension and central obesity ($BMI \geq 25$). The detailed presentation of how confounding variables were selected has been added into the methods (page 11, line 11-12). Furthermore, a Korea population-based study also has performed a cross-sectional-designed observation to explore the relationship between NAFLD and colorectal polyps. This study also selected similar confounding variables (such as age, sex, smoking, NAFLD,

MS but not BMI) and published in the Journal of Gastroenterology and Hepatology^[1].

Other studies also published using the similar methods^[2, 3].

Reviewer #2

Reviewer's code: 03477256

COMMENTS TO AUTHORS

The current manuscript investigated features of the metabolic syndrome (presence of NAFLD) and incidence of adenomatous and hyperplastic polyps. However, there is one relevant limitation: in none of the patients diagnose of NAFLD was not biopsy-proven. I personally do expect a higher incidence of polyps in patients with NASH as compared to simple steatosis in sense of NAFLD.

Response

Thank you for your constructive advice. The most accurate diagnosis of NAFLD was derived by histological information. However, our study was a retrospective clinical research that derived from a routine health check-up database and it is difficult to acquire the histological information from participants. In this study, the diagnosis of fatty live was based on ultrasound imaging with 94% sensitivity and 84% specificity^[4]. Although it may introduce certain bias, we believe that appropriate diagnosis could be established. The presentation of this limitation also has been already added into discussion (page 18, line 11-13). Furthermore, the further prospective study from our center has been established and the biopsy-proven validation would be completed in

the future.

References

- 1 **Hwang ST**, Cho YK, Park JH, Kim HJ, Park DI, Sohn CI, Jeon WK, Kim BI, Won KH, Jin W. Relationship of non-alcoholic fatty liver disease to colorectal adenomatous polyps. *Journal of gastroenterology and hepatology* 2010; **25**(3): 562-567 [PMID: 20074156 DOI: 10.1111/j.1440-1746.2009.06117.x]
- 2 **Yoshida I**, Suzuki A, Vallee M, Matano Y, Masunaga T, Zenda T, Shinozaki K, Okada T. Serum insulin levels and the prevalence of adenomatous and hyperplastic polyps in the proximal colon. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2006; **4**(10): 1225-1231 [PMID: 16979948 DOI: 10.1016/j.cgh.2006.07.002]
- 3 **Huang KW**, Leu HB, Wang YJ, Luo JC, Lin HC, Lee FY, Chan WL, Lin JK, Chang FY. Patients with nonalcoholic fatty liver disease have higher risk of colorectal adenoma after negative baseline colonoscopy. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland* 2013; **15**(7): 830-835 [PMID: 23398678 DOI: 10.1111/codi.12172]
- 4 **Mendler MH**, Bouillet P, Le Sidaner A, Lavoine E, Labrousse F, Sautereau D, Pillegand B. Dual-energy CT in the diagnosis and quantification of fatty liver: limited clinical value in comparison to ultrasound scan and single-energy CT, with special reference to iron overload. *Journal of hepatology* 1998; **28**(5): 785-794 [PMID: 9625313]

