Peer Review File

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Reviewer A:

This paper explores the long-term outcomes of bariatric surgery in patients with Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and severe obesity. This is an important and clinically relevant topic, particularly given the increasing prevalence of obesity and liver disease. However, upon reviewing the paper, several key areas require clarification and improvement. Below are my detailed comments and suggestions:

Comment 1: In the subgroup analysis such as sex group, it is important to ensure that sex is not included as a covariate in the multivariable adjustment, as the analysis is already stratified by this variable. Adjusting for sex in a sex-specific subgroup would result in over-adjustment and could lead to biased or unclear results. I would recommend the authors clarify whether sex was adjusted for in the sex-specific subgroup analyses, and if so, to reconsider this approach.

Reply 1: We appreciate the reviewer's comment. We agree with the reviewer and can confirm that sex was not adjusted for in the sex-specific subgroup analyses. Similarly, we did not adjust for index year and age in their respective subgroup analyses. We apologize for not clarifying this clearly before. We have further described this in the Method section (See page 10, line 198-199) and added this in the footnote of *Supplementary Table 4-6* and *Supplementary Figure 3.*

Changes in the text: Index year, age and sex were not adjusted for in subgroup analyses stratified by each of these specific respective factors.

Comment 2: While PSM has effectively balanced the baseline characteristics, the authors have further adjusted for matched variables (e.g., age, sex) in the multivariable analysis. Although this is common practice for sensitivity analysis, it may introduce over-adjustment risks, particularly when these variables have already been sufficiently balanced after matching.

Reply 2: We agree with the reviewer and can confirm that we did not further adjust for these well-balanced variables such as age, sex etc… in our multivariable Cox regression analyses. We apologize for not clarifying this clearly before. We have clarified this specifically in the Result section (See page 12, line 246-248).

Changes in the text: Because PSM has effectively balanced the relevant baseline characteristics of the study groups, we did not further adjust for these variables in multivariable analysis.

Comment 3: In this study, the authors analyze liver-related outcomes (e.g., cirrhosis, liver decompensation) and non-liver-related outcomes (e.g., cardiovascular disease, chronic kidney disease, and primary obesity-related cancers) as independent endpoints. While these outcomes are analyzed separately, non-liver outcomes (such as severe cardiovascular events or cancers) could potentially impact the occurrence or observation of liver-related outcomes. In such cases, a competing risks model might be more appropriate for handling these interferences. I would suggest the authors provide further clarification on the following: (1) Why a competing risks model was not employed, particularly given the possibility that non-liver outcomes could influence liver outcomes. Could the occurrence of non-liver outcomes (e.g., CVD or cancer) alter or prevent the observation of liver-related events? (2) If the authors believe that these events do not constitute competing risks, it would be helpful to provide a detailed rationale in the methods section, explaining why these outcomes were analyzed independently.

Reply 3: We appreciate the reviewer's comment. The reason that we did not perform competing risks model adjusting for non-liver outcomes (e.g., CVD or cancer) but analyzed non-liver outcomes

independently is that several studies have found when patients develop CVD, CKD or non-liver cancer, they still have possibility to develop cirrhosis or HCC during their lifetime.[1-4] As per the reviewer's suggestion, we have added the above discussion and references to provide a detailed rationale in the Method section to explain why these outcomes were analyzed independently and not in competing risks models (See page 10, line 191-194).

Changes in the text: We did not perform competing risks model adjusting for non-liver outcomes (e.g., CVD or cancer) but analyzed non-liver outcomes independently because several studies have found that when patients develop CVD, CKD or non-liver cancer, they still have possibility to develop cirrhosis or HCC during their lifetime.[1-4]

References

1. Carballo-Folgoso L, Álvarez-Velasco R, Lorca R, et al. Evaluation of cardiovascular events in patients with hepatocellular carcinoma treated with sorafenib in the clinical practice. The CARDIO-SOR study. *Liver Int*. Sep 2021;41(9):2200-2211. doi:10.1111/liv.14941
2. Gundling F, Seidl H, Schmidtler F, et al. Nonhepatic cancer in liver cirrhosis: a retrospective study of prevalence, complication rate after specific oncological treatment, follow-up and prognostic predictors of outcome in 354 patients with cirrhosis. *Anticancer Res*. Sep 2011;31(9):2931-8.
3. Roca-Fernandez A, Banerjee R, Thomaides-Brears H, et al. Liver disease is a significant risk factor for cardiovascular outcomes - A UK Biobank study. *J Hepatol*. Nov 2023;79(5):1085-1095. doi:10.1016/j.jhep.2023.05.046
4. Sarno G, Montalti R, Giglio MC, et al. Hepatocellular carcinoma in patients with chronic renal disease: Challenges of interventional treatment. *Surg Oncol*. Mar 2021;36:42-50. doi:10.1016/j.suronc.2020.11.007

Comment 4: In several key areas of the manuscript, the authors have not provided sufficient references to support their study's background, methodology, and discussion. To improve the academic rigor and credibility of the manuscript, I recommend the authors add some citations：

Feng G, Han Y, Yang W,et al. Recompensation in MASLD-related cirrhosis via metabolic bariatric surgery. Trends Endocrinol Metab. 2024 Jun 21:S1043-2760(24)00159-0. doi: 10.1016/j.tem.2024.05.009. Epub ahead of print. PMID: 38908982.

Lin H, Lee HW, Yip TC, Tsochatzis E, et al. Vibration-Controlled Transient Elastography Scores to Predict Liver-Related Events in Steatotic Liver Disease. JAMA. 2024 Apr 16;331(15):1287-1297. doi: 10.1001/jama.2024.1447. PMID: 38512249; PMCID: PMC10958386.

Reply 4: We appreciate the reviewer's suggestion and have added and discussed the above references as suggested (See page 5, line 75-77 and 93-95).

Changes in the text: 1. Metabolic dysfunction-associated steatotic liver disease (MASLD) is associated with end-stage liver disease as well as nonliver complications such as cardiovascular disease (CVD), chronic kidney disease (CKD) and other nonliver cancers.[5,6]
2. In addition, bariatric surgery may offer the potential for achieving hepatic recompensation in MASLD-related cirrhosis and is getting increasing attention.[7]

References

5. Chan WK, Chuah KH, Rajaram RB, Lim LL, Ratnasingam J, Vethakkan SR. Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): A State-of-the-Art Review. *J Obes Metab Syndr*. Sep 30 2023;32(3):197-213. doi:10.7570/jomes23052
6. Lin H, Lee HW, Yip TC, et al. Vibration-Controlled Transient Elastography Scores to Predict Liver-Related Events in Steatotic Liver Disease. *Jama*. Apr 16 2024;331(15):1287-1297. doi:10.1001/jama.2024.1447
7. Feng G, Han Y, Yang W, et al. Recompensation in MASLD-related cirrhosis via metabolic bariatric surgery. *Trends Endocrinol Metab*. Jun 21 2024;doi:10.1016/j.tem.2024.05.009

Comment 5: While the manuscript discusses the long-term impact of different surgical types on liver and non-liver outcomes, it lacks sufficient comparison with existing literature. The discussion should include a more thorough comparison with prior studies to help explain differences in liver and non-liver-related outcomes between laparoscopic and open surgery.

Reply 5: We appreciate the reviewer's comment; and as suggested, we have added the following paragraph and references to provide additional study context in the Discussion section on (See page 16, line 323-339).

Changes in the text: Laparoscopic bariatric surgery has been associated with more favorable liver outcomes in terms of liver enzyme normalization, liver histology improvement, and overall liver function recovery, possibly due to the less traumatic nature of the surgery and reduced stress and inflammatory response on the liver during recovery compared with open surgery.[8] Consistent with our study, a prior randomized controlled trial compared laparoscopic and open gastric bypass surgery in morbidly obese patients with MASLD and found that the laparoscopic group had more significant reductions in weight loss, liver fat content and improved liver function when compared to open surgery group.[9] Our study also provided important data for the association between laparoscopic surgery and non-liver complications, which may be partly due to the less invasive nature of the procedure, quicker recovery, fewer complications and better control over cardiovascular risk factors such as diabetes and obesity.[10,11] Prior studies have reported fewer long-term complications related to CVD in patients undergoing laparoscopic surgery as compared to open operation.[12,13] However, data comparing laparoscopic vs open bariatric surgery on the long-term outcomes of extrahepatic cancer risk are sparse. Regardless, weight loss achieved through both types of surgery is known to reduce the incidence of certain cancers and laparoscopic surgery tends to have a better long-term recovery and less inflammation response, which may help reducing the likelihood of developing cancer, but further studies are needed.[14,15]

References

8. Schmitz SM, Kroh A, Koch A, et al. Comparison of Liver Recovery After Sleeve Gastrectomy and Roux-en-Y-Gastric Bypass. Obes Surg. Jul 2021;31(7):3218-3226. doi:10.1007/s11695-021-05390-1
9. Nguyen NT, Goldman C, Rosenquist CJ, et al. Laparoscopic versus open gastric bypass: a randomized study of outcomes, quality of life, and costs. Ann Surg. Sep 2001;234(3):279-89; discussion 289-91. doi:10.1097/00000658-200109000-00002
10. Oliveira SC, Neves JS, Souteiro P, et al. Impact of Bariatric Surgery on Long-term Cardiovascular Risk: Comparative Effectiveness of Different Surgical Procedures. Obes Surg. Feb 2020;30(2):673-680. doi:10.1007/s11695-019-04237-0
11. Srinivasan M, Thangaraj SR, Arzoun H, Thomas SS, Mohammed L. The Impact of Bariatric Surgery on Cardiovascular Risk Factors and Outcomes: A Systematic Review. Cureus. Mar 2022;14(3):e23340. doi:10.7759/cureus.23340
12. Benotti PN, Wood GC, Carey DJ, et al. Gastric Bypass Surgery Produces a Durable Reduction in Cardiovascular Disease Risk Factors and Reduces the Long-Term Risks of Congestive Heart Failure. J Am Heart Assoc. May 23 2017;6(5)doi:10.1161/jaha.116.005126
13. Gerber P, Naqqar D, von Euler-Chelpin M, Kauppila JH, Santoni G, Holmberg D. Incidence of Cancer and Cardiovascular Disease After Bariatric Surgery in Older Patients. JAMA Netw Open. Aug 1 2024;7(8):e2427457. doi:10.1001/jamanetworkopen.2024.27457
14. Aminian A, Wilson R, Al-Kurd A, et al. Association of Bariatric Surgery With Cancer Risk and Mortality in Adults With Obesity. Jama. Jun 28 2022;327(24):2423-2433. doi:10.1001/jama.2022.9009
15. Wilson RB, Lathigara D, Kaushal D. Systematic Review and Meta-Analysis of the Impact of Bariatric Surgery on Future Cancer Risk. Int J Mol Sci. Mar 24 2023;24(7)doi:10.3390/ijms24076192

Comment 6: Variables such as race, lifestyle, and socioeconomic status were not included in the matching process, which could influence the outcomes. This should be acknowledged.

Reply 6: We appreciate the reviewer's comment. We acknowledged this in the limitation section (See page 18, line 374-376).

Changes in the text: We did not adjust for additional potential confounders such as race, lifestyle, and socioeconomic status as they were not available in the Marketscan® database, so future studies are needed to evaluate these factors.

Reviewer B:

This is a comprehensive retrospective cohort study comparing long-term outcomes between laparoscopic and open bariatric surgery in patients with severe obesity and MASLD. While the study provides valuable clinical insights, I have several concerns that should be addressed:

Comment 1: The criteria for selecting surgical approach (laparoscopic vs. open) are not clearly described. While propensity score matching was used, unmeasured confounders (surgeon experience, facility characteristics) may still affect the results. I think discussing how these potential selection biases might influence the study findings would be necessary.

Reply 1: We appreciate the reviewer's comment and totally agree with the reviewer. We have added the discussion below to the limitation section and included that we had performed negative control analysis to consider the effect of such potential residual confounding bias with findings suggesting that our results are robust despite the potential presence of unmeasured confounders (See page 18-19, line 384-399).

Changes in the text: Though we adjusted for as many potential confounders associated with adverse outcomes that were available, there may still be some potential unmeasured confounders that were not captured. The criteria for surgical approach selection as unmeasured confounder can vary based on the patient's health and medical history (e.g. severe obesity-related comorbidities, high BMI, abdominal anatomy may be better suited for open surgery) and surgical experience and expertise (e.g. surgeons with extensive experience in laparoscopic techniques and facility support may prefer this method for less complications), as well as patient's preference and risk tolerance (e.g. recovery time and cost).[16] These potential selection biases can lead to an overestimation or underestimation of the benefits of one approach over the other. For example, if laparoscopic surgeries are usually performed by more experienced surgeons or at better-equipped hospitals, the study could incorrectly attribute better outcomes to the laparoscopic approach, when in reality the differences might be due to these confounding factors. Conversely, if open surgery is performed in less experienced surgeons or in less-equipped facilities, its outcomes may appear worse than they truly are. However, we performed additional negative control analyses which suggested that our findings were robust despite the potential presence of unmeasured confounders and residual bias after PSM.

References

16. Eisenberg D, Shikora SA, Aarts E, et al. 2022 American Society of Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) Indications for Metabolic and Bariatric Surgery. *Obes Surg*. Jan 2023;33(1):3-14. doi:10.1007/s11695-022-06332-1

Comment 2: The statement "No missing data need to be addressed" requires further explanation. Please provide detailed information about how missing data was handled in the analysis and potential impact on the results.

Reply 2: We appreciate the reviewer's suggestion and apologize for the lack of clarity on this point. As suggested, we have added the following clarifying details of missing data to the Method section (See page 9-10, line 177-184).

Changes in the text: For continuous variables, we did not have missing data on age and CCI. For categorical variables, sex (female/male), geographic region (Northeast, North central, South, West and Unknown), insurance type (health maintenance organization, preferred provider organization and others), provider specialty (non-gastroenterologist/endocrinologist, gastroenterologist/endocrinologist), year of MASLD diagnosis (2007-2011, 2012-2016 and 2017-2022), year of bariatric surgery (2007-2015 and 2016-2022), the presence of comorbidities (Yes/No) and use of metabolic medications (Yes/No) also did not show any missing data in the database. Thus, no missing data need to be addressed for these variables.

Comment 3: Current analysis focuses only on 30-day complications, and medium-term complications (6 months, 1 year), reoperation rates.

Reply 3: We appreciate the reviewer's comment. As suggested, we have added the following additional complication data in the Result section (See page 12, line 233-237) and in *Supplementary Table 3*: "In regard to medium-term complications, laparoscopic surgery group had lower rate of gastroesophageal reflux disease (0.80% vs. 2.44%), incisional hernia (0.20% vs. 0.81%), chronic diarrhea (0.63% vs. 1.48%), and reoperation rate (0.51% vs. 2.74%), but had higher rate of dumping syndrome (0.24% vs. 0.03%) than open surgery group." We have also added to the limitation section (See page 18, line 379-381) that our study focused on short and medium-term complication rates, so further studies are needed to assess potential differences in the long-term complications of the different bariatric surgical approaches.

Changes in the text: 1. In regard to medium-term complications, laparoscopic surgery group had lower rates of gastroesophageal reflux disease (0.80% vs. 2.44%), incisional hernia (0.20% vs. 0.81%), chronic diarrhea (0.63% vs. 1.48%), and reoperation rate (0.51% vs. 2.74%), but had a higher rate of dumping syndrome (0.24% vs. 0.03%) than open surgery group.
2. Additionally, our study focused on short and medium-term complication rates, so further studies are needed to assess potential differences in the long-term complications of the different bariatric surgical approaches.

Comment 4: In discussion section, it would be necessary to provide more detailed comparison with similar studies, and discuss reasons for any discrepancies with previous findings.

Reply 4: We appreciate the reviewer's suggestion. As suggested, we have added the following paragraph for more detailed study comparison to the Discussion section (See page 16, line 323-339).

Changes in the text: Laparoscopic bariatric surgery has been associated with more favorable liver outcomes in terms of liver enzyme normalization, liver histology improvement, and overall liver function recovery, possibly due to the less traumatic nature of the surgery and reduced stress and inflammatory response on the liver during recovery compared with open surgery.[8] Consistent with our study, a prior randomized controlled trial compared laparoscopic and open gastric bypass surgery in morbidly obese patients with MASLD and found that the laparoscopic group had more significant reductions in weight loss, liver fat content and improved liver function when compared to open surgery group.[9] Our study also provided important data for the association between laparoscopic surgery and non-liver complications, which may be partly due to the less invasive nature of the procedure, quicker recovery, fewer complications and better control over cardiovascular risk factors such as diabetes and obesity.[10,11] Prior studies have reported fewer long-term complications related to CVD in patients undergoing laparoscopic surgery as compared to open operation.[12,13] However, data comparing laparoscopic vs open bariatric surgery on the long-term outcomes of extrahepatic cancer risk are sparse.

Regardless, weight loss achieved through both types of surgery is known to reduce the incidence of certain cancers and laparoscopic surgery tends to have a better long-term recovery and less inflammation response, which may help reducing the likelihood of developing cancer, but further studies are needed.[14,15]

References

8. Schmitz SM, Kroh A, Koch A, et al. Comparison of Liver Recovery After Sleeve Gastrectomy and Roux-en-Y-Gastric Bypass. Obes Surg. Jul 2021;31(7):3218-3226. doi:10.1007/s11695-021-05390-1
9. Nguyen NT, Goldman C, Rosenquist CJ, et al. Laparoscopic versus open gastric bypass: a randomized study of outcomes, quality of life, and costs. Ann Surg. Sep 2001;234(3):279-89; discussion 289-91. doi:10.1097/00000658-200109000-00002
10. Oliveira SC, Neves JS, Souteiro P, et al. Impact of Bariatric Surgery on Long-term Cardiovascular Risk: Comparative Effectiveness of Different Surgical Procedures. Obes Surg. Feb 2020;30(2):673-680. doi:10.1007/s11695-019-04237-0
11. Srinivasan M, Thangaraj SR, Arzoun H, Thomas SS, Mohammed L. The Impact of Bariatric Surgery on Cardio vascular Risk Factors and Outcomes: A Systematic Review. Cureus. Mar 2022;14(3):e23340. doi:10.7759/cureus.23340
12. Benotti PN, Wood GC, Carey DJ, et al. Gastric Bypass Surgery Produces a Durable Reduction in Cardiovascular Disease Risk Factors and Reduces the Long-Term Risks of Congestive Heart Failure. J Am Heart Assoc. May 23 2017;6(5)doi:10.1161/jaha.116.005126
13. Gerber P, Naqqar D, von Euler-Chelpin M, Kauppila JH, Santoni G, Holmberg D. Incidence of Cancer and Cardiovascular Disease After Bariatric Surgery in Older Patients. JAMA Netw Open. Aug 1 2024;7(8):e2427457. doi:10.1001/jamanetworkopen.2024.27457
14. Aminian A, Wilson R, Al-Kurd A, et al. Association of Bariatric Surgery With Cancer Risk and Mortality in Adults With Obesity. Jama. Jun 28 2022;327(24):2423-2433. doi:10.1001/jama.2022.9009
15. Wilson RB, Lathigara D, Kaushal D. Systematic Review and Meta-Analysis of the Impact of Bariatric Surgery on Future Cancer Risk. Int J Mol Sci. Mar 24 2023;24(7)doi:10.3390/ijms24076192

Comment 5: The Discussion section requires substantial expansion regarding the mechanisms underlying the superior outcomes of laparoscopic surgery compared to open surgery, including impact of surgical invasiveness, technical advantages.

Reply 5: We appreciate the reviewer's comment. As suggested, we have added the following discussion and references (See page 16, line 323-326 and line 330-333) to explain the underlying mechanisms about the superior outcomes of laparoscopic surgery compared to open surgery.

Changes in the text: Laparoscopic bariatric surgery has been associated with more favorable liver outcomes in terms of liver enzyme normalization, liver histology improvement, and overall liver function recovery, possibly due to the less traumatic nature of the surgery and reduced stress and inflammatory response on the liver during recovery compared with open surgery.[8] Our study also provided important data for the association between laparoscopic surgery and non-liver complications, which may be partly due to the less invasive nature of the procedure, quicker recovery, fewer complications and better control over cardiovascular risk factors such as diabetes and obesity.[10,11]

References

8. Schmitz SM, Kroh A, Koch A, et al. Comparison of Liver Recovery After Sleeve Gastrectomy and Roux-en-Y-Gastric Bypass. *Obes Surg*. Jul 2021;31(7):3218-3226. doi:10.1007/s11695-021-05390-1
10. Oliveira SC, Neves JS, Souteiro P, et al. Impact of Bariatric Surgery on Long-term Cardiovascular Risk: Comparative Effectiveness of Different Surgical Procedures. *Obes Surg*. Feb 2020;30(2):673-680. doi:10.1007/s11695-019-04237-0
11. Srinivasan M, Thangaraj SR, Arzoun H, Thomas SS, Mohammed L. The Impact of Bariatric Surgery on Cardiovascular Risk Factors and Outcomes: A Systematic Review. *Cureus*. Mar 2022;14(3):e23340. doi:10.7759/cureus.23340

Reviewer C:

A rigorous PSM with a large sample size, nicely done. I have a few comments:

Comment 1: Although I do not expect you do redo any of your analysis, I would encourage your group to look into entropy balancing as an alternative to propensity matching in future observational research

Reply 1: We appreciate the reviewer's suggestion. Entropy balancing is indeed an alternative to propensity score matching for addressing selection bias in observational research.[17] Unlike propensity score matching, which pairs treated and control units based on their propensity scores, entropy balancing directly adjusts the weights of the units to achieve covariate balance between treated and control groups. Entropy balancing can be more robust when there are concerns about unmeasured confounding of the propensity score model.[18] In future observational research, we will consider experimenting with entropy balancing as a complementary method to propensity score matching, especially for studies where covariate balance is crucial for drawing valid conclusions. We have also added this to the limitation section (See page 19, line 399-400). Thank you so much for this suggestion, we really appreciate it.

Changes in the text: In addition, entropy balancing can also be a complementary method to PSM for addressing unmeasured confounding in future studies.[18]

References

17. Chen J, Zhou Y. Causal effect estimation for multivariate continuous treatments. *Biom J*. Jun 2023;65(5):e2200122. doi:10.1002/bimj.202200122
18. Zagar AJ, Kadziola Z, Lipkovich I, Faries DE. Evaluating different strategies for estimating treatment effects in observational studies. *J Biopharm Stat*. 2017;27(3):535-553. doi:10.1080/10543406.2017.1289953

Comment 2: Recently in the journal Obesity Surgery a decision analysis was published by Rouhi et al demonstrating potential for bariatric surgery to reduce the need for liver transplant in NASH patients due to fibrosis regression. Please place this reference in your Discussion section and comment on it based on the findings of your study. This will help elevate the paper with more recent literature and expand the scope of the Discussion to include transplantation.

Reply 2: We appreciate the reviewer's suggestion for this useful reference. As suggested, we have added the following paragraph about this reference based on our findings in the Discussion section (See page 15, line 309-313).

Changes in the text: Recent evidence from a decision analysis study by Rouhi et al. found that surgical weight loss was associated with a reduction in the progression of MASH, thereby reducing the need for liver transplant.[19] The results of this decision analysis align with our study's findings by underscoring the benefit of bariatric surgery on the long-term outcomes with the reduction of end-stage liver disease and liver transplant.

References

19. Rouhi AD, Castle RE, Hoeltzel GD, et al. Sleeve Gastrectomy Reduces the Need for Liver Transplantation in Patients with Obesity and Non-Alcoholic Steatohepatitis: a Predictive Model. *Obes Surg*. Apr 2024;34(4):1224-1231. doi:10.1007/s11695-024-07102-x