Editorial Commentary

Minimally invasive liver resection in metabolic syndrome: insights and future directions

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Hepatocellular carcinoma (HCC) has emerged as a formidable global health challenge since it ranks the sixth most common malignant tumor and the third most common cause of cancer-related death (1). One of the most important factors in the creation of the increased incidence of HCC is the increasing rate of metabolic syndrome (MS), which is a complex interaction of metabolic abnormalities represented by obesity, insulin resistance, dyslipidemia, and hypertension. It was believed that chronic hepatitis B and C were one of the major etiologies of HCC, but additionally, the changed landscape of etiology now points toward MS and its comorbidities, such as non-alcoholic fatty liver disease, as major contributors in promotion of development and progress of HCC (2,3).

Surgical resection remains a fundamental for the HCC treatment, and its application in patients with MS warrants careful consideration (4-6). Berardi *et al.*'s recent study in *Annals of Surgery* provides valuable insights into the comparison of minimally invasive liver resection (MILR) and open liver resection (OLR) in this patient population (7). To our knowledge, this large-scale, multicenter study is the first to focus on patients with MS-related HCC, a subgroup often burdened with multiple comorbidities and higher surgical risks, in whom the benefits of minimally invasive approach may be more pronounced. The authors deserve commendation for their diligent efforts in conducting this extensive study with a substantial sample size and a prolonged follow-up period, lending greater credibility to their findings compared to previous single-center, retrospective analyses with limited cases.

These previous studies have proven that it is appropriate to compare outcome differences between MILR and OLR in different subcategories of patient subgroups and tumor characteristics (8-13), making Berardi *et al.*'s study unique because it squarely falls into this rather special population of MS-related HCC. More importantly, through clearer data collection and analysis, this study further validates the beneficial effect of MILR on reducing complications and ensures that the long-term oncological outcomes published in this study are comparable. To clarify, it is pleasantly surprising how well it is detailed in terms of baseline characteristics, operative outcomes, and long-term survival rates elaborated. The incidence rates of postoperative complications are quite well reported in the supplement materials, hence making the reporting rather transparent and reproducible.

However, it should also be noted that the continuously

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changing diagnostic criteria for MS over this nearly three-decade study period will carry with them potential biases. The authors could make their study more transparent by including a supplemental table in which specific diagnostic criteria are listed for use in all participating centers, and the resulting potential impact on study results that might be expected with such changes is discussed. Even more than that, the diagnostic criteria for MS are different among different places and ethnicities; this fact, in turn, may compromise the generalizability of the findings to other populations. Future studies should consider employing standardized diagnostic criteria, such as those proposed by the International Diabetes Federation or the National Cholesterol Education Program Adult Treatment Panel III, to facilitate comparisons and meta-analyses (14).

An important strength of the study is the use of inverse probability weighting (IPW) to address baseline differences between MILR and OLR groups. However, the limitations of the IPW method, as well as the possibility of residual confounding, should be taken into account when interpreting results (15). For instance, if the calculation of weights does not include important prognostic variables for which the adjustment is being done—liver cirrhosis, tumor staging, and operative time—that can bias results, failing to recognize this would be a great weakness. In addition, the IPW method assumes that all relevant confounders have been measured and considered in the model; this may not always consistently be realized across the board in a retrospective study. Expanding the discussion on the merits and drawbacks of IPW, with reference to relevant methodological literature, would further enrich the article.

An interesting finding in the MILR group is their low rate of complications, which calls for an explanation due primarily to underlying biological mechanisms. Characteristics of minimally invasive surgery, including reduced tissue trauma, diminished liver traction, decreased blood loss, and minimal bowel manipulation, may contribute to a milder stress response and less suppressive immune function (16). These factors would be particularly applicable for patients with MS, who often have both a higher baseline inflammatory state and impaired immune function (17). Further discussion of these potential mechanisms may help to explain the potential benefits of MILR in this specific patient population. Additionally, it would make the study of considerable interest if future basic research focused on the effects it discusses.

Another aspect that is also interesting to debate is the potential impact of the learning curve over the results with the adoption of MILR. Since a period accounting for almost three decades is covered, very probably experience and performance with MILR were very different among the participating surgeons over time, thus bringing in the improved results now being noted in the group receiving MILR, especially at the end of the study period. For this learning curve effect, the authors should consider a subgroup analysis stratified by time periods or by the experience of the surgeon. It is also believed that more detailing regarding the training and credentialing among the center of MILR may help to locate the findings and guide future efforts in their implementations.

In conclusion, the work by Berardi *et al.* is an important step forward in understanding the possible benefits accruable through MILR to patients with MS-related HCC. Such data further strengthen the application of this technique for high-risk patients' surgeries and correctly calls for prospective randomized controlled trials validation for these findings. This leads to the potential for other studies based on this successful trial, which would include high-benefit MILR patients as subgroup analyses to detect them, a cost-effectiveness comparison between MILR and other alternative therapies, and a comparison of the efficacy of a laparoscopic and robotic approach. In this regard, cost-effectiveness studies on the use of MILR for HCC associated with MS will provide crucial information to health decision makers. This will enable further studies to be built on solid ground based on the findings elaborated in this study by Berardi *et al.* and then further plan the surgical management of HCC in the presence of MS. Ultimately, this line of research has the potential to improve patient outcomes, optimize resource allocation, and inform evidence-based guidelines for the treatment of this increasingly prevalent and challenging disease.

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References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024;74:229-63.
2. Llovet JM, Willoughby CE, Singal AG, et al. Nonalcoholic steatohepatitis-related hepatocellular carcinoma: pathogenesis and treatment. Nat Rev Gastroenterol Hepatol 2023;20:487-503.
3. Wang MD, Diao YK, Yao LQ, et al. Emerging role of molecular diagnosis and personalized therapy for hepatocellular carcinoma. iLIVER 2024;3:100083.
4. Wang MD, Tang SC, Li C, et al. Association of Concurrent Metabolic Syndrome with Long-term Oncological Prognosis Following Liver Resection for Hepatocellular Carcinoma Among Patients with Chronic Hepatitis B Virus Infection: A Multicenter Study of 1753 Patients. Ann Surg Oncol 2023;30:346-58.
5. Wang MD, Shen F, Zeng YY, et al. ASO Author Reflections: Effect of Preoperative Metabolic Syndrome for Patients with Hepatocellular Carcinoma. Ann Surg Oncol 2023;30:359-60.
6. Yang T, Hu LY, Li ZL, et al. Liver Resection for Hepatocellular Carcinoma in Non-alcoholic Fatty Liver Disease: a Multicenter Propensity Matching Analysis with HBV-HCC. J Gastrointest Surg 2020;24:320-9.
7. Berardi G, Ivanics T, Sapisochin G, et al. Minimally Invasive Versus Open Liver Resections for Hepatocellular Carcinoma in Patients With Metabolic Syndrome. Ann Surg 2023;278:e1041-7.
8. Nomi T, Hirokawa F, Kaibori M, et al. Laparoscopic versus open liver resection for hepatocellular carcinoma in elderly patients: a multi-centre propensity score-based analysis. Surg Endosc 2020;34:658-66.
9. Troisi RI, Berardi G, Morise Z, et al. Laparoscopic and open liver resection for hepatocellular carcinoma with Child-Pugh B cirrhosis: multicentre propensity score-matched study. Br J Surg 2021;108:196-204.
10. Miyama A, Morise Z, Aldrighetti L, et al. Multicenter Propensity Score-Based Study of Laparoscopic Repeat Liver Resection for Hepatocellular Carcinoma: A Subgroup Analysis of Cases with Tumors Far from Major Vessels. Cancers (Basel) 2021;13:3187.
11. Yoon YI, Kim KH, Cho HD, et al. Operative and long-term oncologic outcomes of laparoscopic versus open major liver resection in patients with a high body mass index (>25 kg/m2): a propensity score matching analysis. Surg Endosc 2022;36:5772-83.
12. Zimmitti G, Sijberden JP, Osei-Bordom D, et al. Indications, trends, and perioperative outcomes of minimally invasive and open liver surgery in non-obese and obese patients: An international multicentre propensity score matched retrospective cohort study of 9963 patients. Int J Surg 2022;107:106957.
13. Krenzien F, Schmelzle M, Pratschke J, et al. Propensity Score-Matching Analysis Comparing Robotic Versus Laparoscopic Limited Liver Resections of the Posterosuperior Segments: An International Multicenter Study. Ann Surg 2024;279:297-305.
14. Huang PL. A comprehensive definition for metabolic syndrome. Dis Model Mech 2009;2:231-7.
15. Elze MC, Gregson J, Baber U, et al. Comparison of Propensity Score Methods and Covariate Adjustment: Evaluation in 4 Cardiovascular Studies. J Am Coll Cardiol 2017;69:345-57.
16. Ciria R, Cherqui D, Geller DA, et al. Comparative Short-term Benefits of Laparoscopic Liver Resection: 9000 Cases and Climbing. Ann Surg 2016;263:761-77.
17. Hotamisligil GS. Inflammation and metabolic disorders. Nature 2006;444:860-7.

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