Editorial

Poor prognosis of hepatocellular carcinoma patients—how, why, and what?

Vishal G. Shelat^

Department of General Surgery, Tan Tock Seng Hospital, Singapore, Singapore

Correspondence to: Vishal G. Shelat, FRCS (Ed), FEBS (HPB Surgery). Adjunct Associate Professor, Department of General Surgery, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433, Singapore. Email: vgshelat@rediffmail.com.

Comment on: Zhou W, Ye F, Yang G, *et al.* YAP-based nomogram predicts poor prognosis in patients with hepatocellular carcinoma after curative surgery. J Gastrointest Oncol 2024. doi: 10.21037/jgo-24-36.

Keywords: Hepatocellular carcinoma (HCC); Hippo pathway; Yes-associated protein (YAP)

Submitted Aug 05, 2024. Accepted for publication Aug 20, 2024. Published online Oct 12, 2024.
doi: 10.21037/jgo-24-595
View this article at: https://dx.doi.org/10.21037/jgo-24-595

The late Dr. Blake Cady's well-known quote at the presidential address to the Society of Surgical Oncology in 1988 "*Biology is king; case selection is the queen, and technical maneuvers undertaken are the princes and princesses of the realm.*" is highly relevant to hepatocellular carcinoma (HCC) treatment landscape with post resection recurrence being very common. Recurrence is a dominant aetiology for cancer related mortality. Those who escape this mortality, liver dysfunction and treatment related morbidity delivers the final blow to the survival chances, which thankfully a few can escape. It remains the efforts of both bench and bedside researchers to increase the pool of people who can enjoy additional years of healthy life with precision person-centered care administered by multidisciplinary teams and delivered by high reliable healthcare systems within the state which ensure accessible and affordable care without barriers and eliminating any health disparities. Thus, the retrospective study originating from Eastern Hepatobiliary Surgery Hospital in Shanghai by Zhou *et al.* reporting the importance of Yes-associated protein (YAP) in predicting recurrence and poor prognosis of patients treated by liver resection is very relevant, as it serves to testify Dr. Cady's quote (1). This editorial shall not delve into the criticism of single-centre origin, retrospective design, small sample size, or predominant hepatitis B aetiology of the study population, but rather decipher the results and its implications in surgical decision-making. Similarly, this editorial shall not discuss the interesting associations observed and reported by Zhou *et al.* suggesting that hepatitis B virus may cause HCC via YAP related mechanisms, and YAP pathway has a role in secretion of alpha fetoprotein (1). I have elected to discuss and highlight four issues to serve to stimulate the clinician readers.

Firstly, for the benefit of clinicians and surgical colleagues, I summarize the Hippo signalling pathway mechanism and its relevance with YAP in HCC patients. The Hippo signalling pathway is a critical regulatory pathway that controls organ size, cell proliferation, and differentiation in many organisms, including humans. It plays a fundamental role in tissue homeostasis and development by preventing excessive cell growth and promoting apoptosis. Disruption of this pathway is linked to various cancers and other diseases, including HCC (2). The core components of the Hippo pathway include the serine/threonine kinases Mammalian Ste20-like protein kinase 1 (MST1) and MST2, which are activated by various stimuli, such as cell density and extracellular cues. When activated, MST1/2 phosphorylate and activate the downstream kinase Large tumor suppressor kinase 1 (LATS1) and LATS2. These kinases further phosphorylate the transcriptional co-activator YAP, leading to their sequestration in the cytoplasm and subsequent degradation. When the Hippo

^ ORCID: 0000-0003-3988-8142.

pathway is active, YAP is kept in check, preventing it from translocating into the nucleus, where it promotes the expression of genes involved in cell growth and survival. Conversely, when the Hippo pathway is inactive, YAP translocate to the nucleus, driving the expression of proliferative and anti-apoptotic genes. This mechanism is crucial in preventing tumours, as unregulated YAP activity can lead to unchecked cellular proliferation and resistance to apoptosis (3). The Hippo pathway is also involved in other important processes such as stem cell regulation, wound healing, and organ regeneration (4). YAP is a key transcriptional co-activator that interacts with several transcription factors to regulate gene expression, primarily in response to signals from the Hippo signalling pathway. As a central component of this pathway, YAP plays a crucial role in controlling cell growth, proliferation, and apoptosis, making it a significant player in developmental biology and tumorigenesis. YAP is typically localized in the cytoplasm when the Hippo pathway is active, primarily due to the phosphorylation by LATS kinases. However, when the Hippo pathway is inhibited or dysregulated, YAP enters the nucleus, where it interacts with various transcription factors to drive the expression of genes that promote cell growth and survival. The aberrant activation of YAP is linked to several human cancers, including liver, breast, and colorectal cancers (5). In these contexts, YAP can promote tumorigenesis by enhancing cell proliferation, inhibiting apoptosis, and driving epithelial-to-mesenchymal transition (EMT). Moreover, understanding YAP's interactions and regulatory mechanisms is essential for elucidating its potential as a therapeutic target in cancer treatment and drug resistance (6).

Secondly, Zhou *et al.* report the following six variables as predicting recurrence after surgical resection: tumor size, Child-Pugh score, microvascular invasion (MVI), hepatitis B surface antigen positivity, tumor grade, and YAP positivity (1). Tumor size is directly proportional to tumor volume (7). Large size increases the proximity to major vessels with higher propensity of MVI and increases technical difficulty with higher operative blood loss or close resection margins (8). HCC size did not receive the same attention in tumor staging systems until much recently, and it is apt that Zhou *et al.* report endorses the importance of size in predicting surgical outcomes. Regarding Child-Pugh score, in most reports, about 10% of liver resection patients belong to Child-Pugh grade B (9). Zhou *et al.*'s study reports 9.2% (n=24/262) and thus reflects real-world scenario. In patients with Child-Pugh grade B, major liver resection must be performed cautiously to reduce risk of post hepatectomy liver failure (PHLF), hence precision surgery using novel technological adjuncts is integral to ensure good perioperative outcomes (10). The utility of pre-operative indocyanine green dye retention and managing the six—Ts: time (surgical), transfusion (blood loss), temper (keep calm), technology (use it to one's advantage), teamwork (scrub nurse, surgical assistant), and talking (communication with anaesthetist) are useful in my personal experience. Regarding MVI, a common understanding is essential as it is associated with poor overall survival (OS) in HCC patients. Cong *et al.* defines MVI as invasion of tumor cells in a named vein partially or totally lined by endothelial cells visible only by microscopy of specimens (11). Additionally, they propose a three-tiered grading system, classifying specimens as M0 (no MVI), M1 (1–5 sites of MVI, located at ≤1 cm away from the tumor-adjacent liver tissue) and M2 (>5 MVI sites or at >1 cm away from the tumor-adjacent liver tissue). Though Zhou *et al.* did not grade the MVI level, in my opinion, MVI is a post-operative variable, like the YAP status, and thus have minimal impact in surgical decision-making for resection versus alternative options of treatment. Though, a model with all preoperative variables is desirable as it enables decision-making, such a model may lack the predictive power without the additional information about the tumour biology which is derived from pathological analysis of specimens (refer to Dr. Cady's quote above). I shall not discuss the YAP status as Zhou *et al.* has already elaborated it their manuscript and I do not need to undermine their efforts by repeating it.

The third point of discussion relates to the findings that nomogram including YAP status predicts not only recurrence-free survival (RFS), but also OS. This is highly significant considering that very often RFS is reported as a surrogate of OS in clinical oncology trials. The recurrence rate for YAP-high (n=67) and YAP-low (n=12) and the mortality rate for YAP-high (n=37) and YAP-low (n=2) at 12 months is worth discussing [data obtained from *Fig. 1* of Zhou *et al.* (1)]. About 15% patients (n=39/262) died within 1-year of liver resection. This is higher compared to a 9.2% from a local institution from Singapore (12). While this editorial is not about pitching one institution or country against other, the fact remains that 1-year mortality is an important outcome which is often neglected and unreported in surgical reports, including the landmark report on textbook outcomes following liver surgery. Timothy Pawlik and colleagues report the following as textbook outcome when a patient experienced the following five goals:

negative-margin liver resection; no serious postoperative complications (Clavien-Dindo ≥3); no 30-day readmission; no 30-day mortality; and no prolonged length of stay (LOS) (13,14). One-year mortality is not included as a key quality metric for textbook outcome; probably as it is too distant outcome and surgical community places it outside the realm of perioperative outcome and within the realm of oncological outcome. However, most oncological outcomes also report 2-, 3- or 5-year survival outcomes, like Zhou *et al.*'s report (1). Thus, the 1-year survival remains a neglected stepchild of modern surgical oncology which neither surgeons nor medical oncologists' trend or report diligently. In my viewpoint, this is an important quality metric as it highlights a group of patients (about 10–15%) who could have been managed (probably) without surgery, thus reducing the patient's pain and suffering towards the end of life and saving the opportunistic cost to the society. This is important considering that a combination of trans-arterial chemoembolization (TACE) with radiofrequency ablation has similar oncologic outcomes as surgical resection (15).

Lastly, regarding the clinical impact of the study findings, it is essential to consider the patient selection for adjuvant therapy after surgical resection of HCC. In a systematic review and meta-analysis of 40 studies [10 randomized control trials (RCTs) and 30 non-RCTs] including 11,165 patients, Chen *et al.* reported that postoperative adjuvant TACE was associated with an increased OS [hazard ratio (HR), 0.71; 95% confidence interval (CI): 0.65–0.77; P<0.001] and the effect was prominent in the subgroup of patients with MVI, tumor size >5 cm or multinodular tumors (16). Hepatic arterial infusion chemotherapy (HAIC) is an emerging theme in HCC arena (17). Moran *et al.* reported a meta-analysis of 11 retrospective cohort studies including 680 patients (n=325 patients in resection followed by adjuvant HAIC and n=355 in resection alone group) and adjuvant HAIC improved the 1-year [relative risk (RR), 0.54; 95% CI: 0.31–0.94; P=0.030], 3-year (RR, 0.53; 95% CI: 0.41–0.69; P<0.01), and 5-year (RR, 0.69; 95% CI: 0.58–0.83; P<0.01) OS of resected HCC patients (18). This effect was evident across all/any tumor size. In a recent network meta-analysis reporting 23 trials including 3,940 patients treated by eight different adjuvant treatment protocols, authors reported that the addition of adjuvant therapy lowers the risk of recurrence and provide survival benefit after surgical resection for HCC (19). Zhou *et al.* report a nomogram and not a risk variable. The nomogram provides a guide regardless of the YAP positive or negative status, and thus their report has credibility with a potential for bed-side application if resources and expertise exist for immunohistochemical assessment and identification with quantification of YAP in resected specimens.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Gastrointestinal Oncology*. The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-595/coif). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Zhou W, Ye F, Yang G, et al. YAP-based nomogram predicts poor prognosis in patients with hepatocellular carcinoma after curative surgery. J Gastrointest Oncol 2024. doi: 10.21037/jgo-24-36.
2. Li S, Hao L, Li N, et al. Targeting the Hippo/YAP1 signaling pathway in hepatocellular carcinoma: From mechanisms to therapeutic drugs (Review). Int J Oncol 2024;65:88.
3. Li N, Liu YH, Wu J, et al. Strategies that regulate Hippo signaling pathway for novel anticancer therapeutics. Eur J Med Chem 2024;276:116694.

4. Cao J, Su Z, Zhang Y, et al. Turning sublimed sulfur and bFGF into a nanocomposite to accelerate wound healing via co-activate FGFR and Hippo signaling pathway. Mater Today Bio 2024;26:101104.
5. Mo H, Li R, Yang N, et al. USP40 promotes hepatocellular carcinoma progression through a YAP/USP40 positive feedback loop. Cancer Lett 2024;589:216832.
6. Mo C, You W, Rao Y, et al. Epigenetic regulation of DNA repair gene program by Hippo/YAP1-TET1 axis mediates sorafenib resistance in HCC. Cell Mol Life Sci 2024;81:284.
7. Wee JJ, Tee CL, Junnarkar SP, et al. Outcomes of surgical resection of super-giant (≥15 cm) hepatocellular carcinoma: Volume does matter, if not the size. J Clin Transl Res 2022;8:209-17.
8. Lee AJ, Wu AG, Yew KC, et al. Does size matter for resection of giant versus non-giant hepatocellular carcinoma? A meta-analysis. World J Gastrointest Surg 2023;15:273-86.
9. Kabir T, Ye M, Mohd Noor NA, et al. Preoperative Neutrophil-to-Lymphocyte Ratio Plus Platelet-to-Lymphocyte Ratio Predicts the Outcomes after Curative Resection for Hepatocellular Carcinoma. Int J Hepatol 2019;2019:4239463.
10. Lim JSH, Shelat VG. 3D laparoscopy and fluorescence imaging can improve surgical precision for hepatectomy. Hepatobiliary Surg Nutr 2024;13:544-7.
11. Cong WM, Bu H, Chen J, et al. Practice guidelines for the pathological diagnosis of primary liver cancer: 2015 update. World J Gastroenterol 2016;22:9279-87.
12. Sheriff S, Madhavan S, Lei GY, et al. Predictors of mortality within the first year post-hepatectomy for hepatocellular carcinoma. J Egypt Natl Canc Inst 2022;34:14.
13. Merath K, Chen Q, Bagante F, et al. Textbook Outcomes Among Medicare Patients Undergoing Hepatopancreatic Surgery. Ann Surg 2020;271:1116-23.
14. Tsilimigras DI, Sahara K, Moris D, et al. Assessing Textbook Outcomes Following Liver Surgery for Primary Liver Cancer Over a 12-Year Time Period at Major Hepatobiliary Centers. Ann Surg Oncol 2020;27:3318-27.
15. Gui CH, Baey S, D'cruz RT, et al. Trans-arterial chemoembolization + radiofrequency ablation versus surgical resection in hepatocellular carcinoma - A meta-analysis. Eur J Surg Oncol 2020;46:763-71.
16. Chen W, Ma T, Zhang J, et al. A systematic review and meta-analysis of adjuvant transarterial chemoembolization after curative resection for patients with hepatocellular carcinoma. HPB (Oxford) 2020;22:795-808.
17. Lim JSH, Shelat VG. Revolutionizing hepatocellular carcinoma treatment: the advent of a new era of adjuvant therapy. Chin Clin Oncol 2023;12:49.
18. Moran A, Ramos LF, Picado O, et al. Hepatocellular carcinoma: resection with adjuvant hepatic artery infusion therapy vs resection alone. A systematic review and meta-analysis. J Surg Oncol 2019;119:455-63.
19. Liu Y, Wang Y, Guo X, et al. Comparative Effectiveness of Adjuvant Treatment for Resected Hepatocellular Carcinoma: A Systematic Review and Network Meta-Analysis. Front Oncol 2021;11:709278.

Cite this article as: Shelat VG. Poor prognosis of hepatocellular carcinoma patients—how, why, and what? J Gastrointest Oncol 2024;15(5):2372-2375. doi: 10.21037/jgo-24-595