



Advancing prognostic precision in hepatocellular carcinoma: a paradigm shift towards machine learning

Flavio Milana^{1,2}, Simone Famularo^{1,2}, Guido Torzilli^{1,2^}

¹Department of Biomedical Sciences, Humanitas University, Milan, Italy; ²Division of Hepatobiliary and General Surgery, Department of Surgery, IRCCS Humanitas Research Hospital, Milan, Italy

Correspondence to: Guido Torzilli, MD, PhD. Professor & Chairman, Department of Biomedical Sciences, Humanitas University, Via Montalcini 4, 20090 Pieve Emanuele, Milan, Italy; Division of Hepatobiliary and General Surgery, Department of Surgery, IRCCS Humanitas Research Hospital, Via Manzoni 56, 20089 Rozzano, Milan, Italy. Email: guido.torzilli@hunimed.eu.

Comment on: Zeng J, Zeng J, Lin K, *et al.* Development of a machine learning model to predict early recurrence for hepatocellular carcinoma after curative resection. *Hepatobiliary Surg Nutr* 2022;11:176-87.

Keywords: Hepatocellular carcinoma (HCC); machine learning; liver resection; early recurrence

Submitted Jul 19, 2023. Accepted for publication Aug 22, 2023. Published online Sep 11, 2023.

doi: 10.21037/hbsn-23-360

View this article at: <https://dx.doi.org/10.21037/hbsn-23-360>

Introduction

Hepatocellular carcinoma (HCC) stands as a significant contributor to cancer-related mortality, ranking as the fifth leading cause of cancer-related death (1). In 80% of cases, HCC arises from an underlying liver disease (2). Despite screening programs for at-risk patients, the prognosis for HCC remains even dismal because of late diagnosis. The only curative options currently available are liver resection for selected cases, and liver transplantation. However, the high rate of recurrence after surgery makes the prognosis bleak. In fact, following curative intent resection, the 5-year recurrence is approximately 60% (3), with 5-year survival after recurrence of 35% (4).

This highlights the urgent need for improved prognostic indicators and early detection methods. Identifying early recurrences, namely happening within 2 years from liver surgery, is crucial for the possibility of an effective loco-regional treatment such as second liver resection or salvage liver transplantation. Indeed, systemic protocols have demonstrated poor disease control.

The application of a new model for an old problem

In light of this challenging situation, the recently published paper by Zeng *et al.* (5). presents a novel approach to address an old and longstanding problem. The identification of factors capable of predicting early recurrence in patients undergoing curative intent resection is of utmost importance in the era of personalized medicine. The ability to identify a high-risk subgroup, as shown in the paper, would allow for a more strict follow-up and the eventuality of considering these patients for adjuvant chemotherapy protocols, including the promising new immune checkpoint inhibitors (6).

In their remarkable job, the authors developed an interesting prediction tool based on a random survival forest (RSF) model, which not only demonstrates its validity through external validation but also outperforms other well-established models. Indeed, as already reported (7), the limitations of these existing models stem from their reliance on linear assumptions underlying the calculation

[^] ORCID: 0000-0001-5798-5021.

of proportional hazard, which restricts their predictive performance. In line with other milestones in the field of artificial intelligence, such as those by Singal *et al.* (8) or Cucchetti *et al.* (9), Zeng *et al.* demonstrate how the application of machine learning algorithms to forecasting significantly improves the accuracy of predictions. The model's discriminatory power was well evaluated using several methods, including Harrell's C-index, Gonen & Heller's K and time-dependent areas under the receiver operating characteristics curve. Furthermore, the authors successfully stratified patients into three different risk groups, identifying a high-risk category that accounted for 14.6% of the patients but encompassed 86.2% of early recurrences. Notably, the decision curve analysis (DCA) showed superior net benefit compared to other models, providing convincing evidence of its efficacy.

However, some methodological details could have been addressed to enhance the quality of the results. Specifically, handling missing values is an important consideration in data mining due to the abundance of datasets. Imputation techniques could have been employed to mitigate the impact of missing data, as merely removing patients with incomplete clinical data may result in the loss of valuable information. Overfitting represents another potential issue that warrants attention. Although the quality scores obtained for both internal and external validation are impressive, it is crucial to assess the similarities among groups and ascertain whether the model is simply memorizing data rather than learning from them. This is particularly relevant when looking at baseline characteristics of the cohort. More than 80% of cases have hepatitis B virus infection across all groups, either training either internal and validation cohorts. Consequently, careful consideration and validation with other geographic subsets should be undertaken to ensure broader applicability. Indeed this could be the reason why the model considers etiology, liver cirrhosis, and alpha-fetoprotein (AFP) of neglectable importance whereas they could be more relevant in patients with different etiologies as metabolic or alcoholic steatohepatitis. In this optic, validation with an independent group with a different pathological substrate would be beneficial in further confirming the results.

Furthermore, from the variable importance analysis, it emerges that the most important ones are largely beyond the surgical intervention, emphasizing the role of tumor biology on recurrence dynamics and the significance of strict follow-up in specific subgroups of patients other than tailored protocols for the management of the disease.

With no doubts, this paper navigates the uncharted territory of prediction and forecasting, where machine learning models are supposed to dominate in the coming decades. Moreover, as for other recently published algorithms (10), the value of this work is amplified by the availability of a web-based prediction tool, facilitating practical application and easy dissemination.

Conclusions

To conclude, it should be highlighted that the model's indications should be interpreted and translated as supportive information rather than a replacement for the expertise and professionalism of physicians in real-life scenarios. The actual challenge is exactly that of letting the artificial intelligence be embraced by the medical expertise to let the outperforming pupil work with the whole needed information.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-360/coif>). GT serves as an unpaid editorial board member of *Hepatobiliary Surgery and Nutrition*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the

formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021;71:209-49.
2. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003;362:1907-17.
3. Famularo S, Donadon M, Cipriani F, et al. Hepatocellular carcinoma surgical and oncological trends in a national multicentric population: the HERCOLES experience. *Updates Surg* 2020;72:399-411.
4. Erridge S, Pucher PH, Markar SR, et al. Meta-analysis of determinants of survival following treatment of recurrent hepatocellular carcinoma. *Br J Surg* 2017;104:1433-42.
5. Zeng J, Zeng J, Lin K, et al. Development of a machine learning model to predict early recurrence for hepatocellular carcinoma after curative resection. *Hepatobiliary Surg Nutr* 2022;11:176-87.
6. Kudo M. Adjuvant Immunotherapy after Curative Treatment for Hepatocellular Carcinoma. *Liver Cancer* 2021;10:399-403.
7. Ishwaran H, Kogalur UB, Blackstone EH, et al. Random survival forests. *Ann Appl Stat* 2008;2:841-60.
8. Singal AG, Mukherjee A, Elmunzer BJ, et al. Machine learning algorithms outperform conventional regression models in predicting development of hepatocellular carcinoma. *Am J Gastroenterol* 2013;108:1723-30.
9. Cucchetti A, Piscaglia F, Grigioni AD, et al. Preoperative prediction of hepatocellular carcinoma tumour grade and micro-vascular invasion by means of artificial neural network: a pilot study. *J Hepatol* 2010;52:880-8.
10. Famularo S, Donadon M, Cipriani F, et al. Machine Learning Predictive Model to Guide Treatment Allocation for Recurrent Hepatocellular Carcinoma After Surgery. *JAMA Surg* 2023;158:192-202.

Cite this article as: Milana F, Famularo S, Torzilli G. Advancing prognostic precision in hepatocellular carcinoma: a paradigm shift towards machine learning. *HepatoBiliary Surg Nutr* 2023;12(5):810-812. doi: 10.21037/hbsn-23-360