EDITORIAL

Liver Cancer INTERNATIONAL   WILEY

Need for independence of treatment allocation from prognostic evaluation for hepatocellular carcinoma

The complexity of the evaluation of patients with hepatocellular carcinoma (HCC) is related to the need of simultaneously considering – when planning treatment and assessing prognosis – not only the magnitude of tumour burden and the degree of general well-being of patients (i.e. their Performance Status [PS]) as in other malignancies, but also the extent of the concomitant liver dysfunction. Moreover, adding further complications to the difficulties faced in streamlining this complex process, various evidence-based treatments are available to treat patients with HCC. This has led, through the years, to the development of several, variously designed prognostic scores and staging systems, without having yet reached a consensus on the universally accepted best one.

HCC prognostic assessment scores can be divided into two main categories, differing in design characteristics (data based or evidence based), prognostic value, significance in treatment allocation.[1] Evidence-based staging systems (Tumour Nodes Metastasis [TNM], Barcelona Clinic Liver Cancer [BCLC] and Chinese Liver Cancer [CNLC] classifications) are defined based on HCC patients' prognostic evidence from the literature and typically offer a linkage, sometimes univocal, with treatment modalities. Data-based prognostic scores (Okuda staging system, Cancer of the Liver Italian Program [CLIP] score, Japan Integrated Staging [JIS] score, Model to Estimate Survival for HCC [MESH] score], on the other hand, are obtained with rigorous statistical methodology and demonstrated to have a better prognostic performance compared to evidence-based staging systems.[2] Lastly, a third category can also be identified, namely combined prognostic systems, used both as prognostic scores and staging systems. A recent example of one of these systems, based on literature evidence but weighted in a real population, is the Italian Liver Cancer (ITA.LI.CA) prognostic system.[3]

The Hepatocellular Carcinoma Survival Prediction Score (HCC-SPS), proposed by Tan et al. in the current issue of Liver Cancer International, can be categorised as a data-based prognostic score. Indeed, this study is an interesting example of how this kind of scores are created, relying on real-life population data, solid statistical bases, internal and external validation.[4] Noteworthy, the HCC-SPS score incorporates a multitude of parameters in comparison with other HCC survival scores. In addition to tumour characteristics, it also assesses liver functional reserve, the albumin–bilirubin (ALBI) grade and patient's physical functional status. Furthermore, it includes the only humoral parameter which is widely available in clinical practice to assess the 'biological aggressiveness' of HCC, such as alpha-fetoprotein.[5] One of its limits, though, is the scarce numerosity of the external validation populations.

Another limitation of the HCC-SPS is that it needs to be derived from each single-centre data, thus requiring the presence of an HCC database and not being able to prognosticate a universal survival rate. This is clearly demonstrated by the marked difference in the observed overall survival for the same risk category across the various study cohorts. Its validation by more groups is therefore essential to confirm its universal applicability.

One of the more original aspects of this paper was that the HCC-SPS was equally effective without including treatment modality, even though this showed to be a significant independent factor for patient survival in the original analysis. Tan et al. highlight the benefit of the applicability of HCC-SPS at the moment of HCC diagnosis, suggesting that the definition of patient's prognosis independently from treatment can be the preferable approach to the prediction of outcome.[4]

Prognostic evaluation independence from treatment allocation is a well-established concept concerning other malignancies (e.g. Fong's Score in the field of colorectal liver metastases), but is a concept that is still not distinctly accepted in the field of HCC.[6] In this regard, in the manuscript by Tang et al., a comparison of survival prediction using the Akaike information criterion values showed that the HCC-SPS performed better than BCLC although, unfortunately, comparisons with other prognostic systems were not possible.

In the last two decades, an inexplicable anomaly has characterised HCC prognostic stratification and management. This anomaly was the claim to adopt a unique system working simultaneously as a prognostic classification and a treatment algorithm. This system was the evidence-based BCLC classification, which was first presented in 1999 with the aim of classifying HCC patients on the basis of therapeutic perspectives.[7] As above underlined and confirmed in the study by Tan et al.,[4] the BCLC has a lower ability to determine the prognosis of HCC patients, in particular when quite heterogeneous classes, such as the Intermediate and Advanced one, are taken into consideration.[8,9] But the second relevant consequence of the 'BCLC anomaly' was that this classification, as originally presented, was based on a rigid 'stage hierarchy' which uniquely assigned a single specific kind of treatment

to each determined HCC stage. It was observed through the years, though, that the main risk of this strict system was to undertreat patients who might instead have achieved better outcomes if treated with more flexibly sorted therapies.[10] Attempts to introduce more flexibility in treatment allocation for HCC patients were introduced in the recent European Association for the Study of the Liver (EASL) 2018 guidelines (i.e. 'treatment stage migration') and in the American Association Study of the Liver (AASLD) 2018 guidelines (i.e. 'treatment stage alternative') for the management of patients with HCC.[11,12] However, even these attempts do not guarantee the possibility to assign the best therapy to each patient as dictated by the philosophy of precision medicine.[13] More recently, the idea of offering patients the whole array of available treatment in order to pick the best one fitting each specific individual was presented as 'therapeutic hierarchy', which includes two important concepts.[14] First, the existence of a hierarchy of effectiveness between the different available therapy strategies for HCC.[15] Second, but not less importantly, the need of separating HCC staging from treatment modality as suggested by the paper by Tan et al.[4,16] Thus, the current study is a fresh start in the direction of application of therapeutic hierarchy in the management of patients with HCC, and we acknowledge the invitation put forward by the authors that further studies in different settings are needed to assess the universal applicability of their risk score.

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REFERENCES

1. Vitale A, Farinati F, Finotti M, et al. Overview of prognostic Systems for Hepatocellular Carcinoma and ITA.LI.CA external validation of MESH and CNLC classifications. *Cancer*. 2021;13(7):1673. doi:10.3390/cancers13071673
2. Liu PH, Hsu CY, Hsia CY, et al. Prognosis of hepatocellular carcinoma: assessment of eleven staging systems. *J Hepatol*. 2016;64(3):601-608. doi:10.1016/j.jhep.2015.10.029
3. Farinati F, Vitale A, Spolverato G, et al. Development and validation of a new prognostic system for patients with hepatocellular carcinoma. *PLOS Med*. 2016;13(4):e1002006. doi:10.1371/journal.pmed.1002006
4. Tan TJ, Shen L, Hajiev S, et al. Development and validation of a therapy-independent hepatocellular carcinoma survival prediction score. *Liver Cancer Int*. 2022:1-8. doi:10.1002/lci2.45
5. Giannini EG, Sammito G, Farinati F, et al. Determinants of alpha-fetoprotein levels in patients with hepatocellular carcinoma: implications for its clinical use. *Cancer*. 2014;120(14):2150-2157. doi:10.1002/cncr.28706
6. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg*. 1999;230(3):309. doi:10.1097/00000658-199909000-00004
7. Llovet J, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis*. 1999;19(03):329-338. doi:10.1055/s-2007-1007122
8. Giannini EG, Moscatelli A, Pellegatta G, et al. Application of the intermediate-stage subclassification to patients with untreated hepatocellular carcinoma. *Am J Gastroenterol* 2016;111(1):70–77. doi:10.1038/ajg.2015.389
9. Giannini EG, Bucci L, Garuti F. Patients with advanced hepatocellular carcinoma need a personalized management: a lesson from clinical practice. *Hepatology*. 2018 May;67(5):1784-1796. doi:10.1002/hep.29668
10. Farinati F, Vanin V, Giacomin A, et al. BCLC stage B hepatocellular carcinoma and transcatheter arterial chemoembolization: a 20-year survey by the Italian liver cancer group. *Liver Int*. 2015;35(1):223-231. doi:10.1111/liv.12649
11. Galle PR, Forner A, Llovet JM, et al. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2018;69(1):182-236. doi:10.1016/j.jhep.2018.03.019
12. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and Management of Hepatocellular Carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases: Marrero et al. *Hepatology*. 2018;68(2):723-750. doi:10.1002/hep.29913
13. Pinato DJ. A pathway towards precision: setting the agenda for liver cancer international. *Liver Cancer Int*. 2020;1(1):5. doi:10.1002/lci2.7
14. Vitale A, Trevisani F, Farinati F, Cillo U. Treatment of hepatocellular carcinoma in the precision medicine era: from treatment stage migration to therapeutic hierarchy. *Hepatology*. 2020;72(6):2206-2218. doi:10.1002/hep.31187
15. Vitale A, Farinati F, Pawlik TM, et al. The concept of therapeutic hierarchy for patients with hepatocellular carcinoma: a multicenter cohort study. *Liver Int*. 2019;39(8):1478-1489. doi:10.1111/liv.14154
16. Vitale A, Finotti M, Trevisani F, Farinati F, Giannini EG. Treatment allocation in patients with hepatocellular carcinoma: Need for a paradigm shift? *Liver Cancer Int*. 2022;3:34-36. doi:10.1002/lci2.42