DR. TEH-IA HUO (Orcid ID : 0000-0003-2202-521X)

DR. PO-HONG LIU (Orcid ID : 0000-0001-6205-3704)

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Correspondence

Using circulating biomarkers to stage hepatocellular carcinoma: Pitfalls and limitations

Teh-Ia Huo, MD,[1,2,3] Po-Hong Liu, MD, MPH[2,4] Chia-Yang Hsu, MD, MPH[2,5]

[1]Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan;

[2]Faculty of Medicine, [3]Institute of Pharmacology, National Yang-Ming University School of Medicine, Taipei, Taiwan;

[4]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA;

[5] Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, MI, USA

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Correspondence:

Teh-Ia Huo, M.D.

Department of Medical Research

Taipei Veterans General Hospital

Taipei, Taiwan

Tel: + 886 2 2871 2121

Fax: + 886 2 2873 9318

Email: tihuo@vghtpe.gov.tw

To the Editor:

We read with interest the paper "HepatoScore-14: Measures of biological heterogeneity significantly improve prediction of hepatocellular carcinoma risk" by Dr. Morris *et al.* published in an upcoming issue of Hepatology.[1] It is an elegant study looking at the feasibility of using a new set of biomarkers, the HepatoScore-14, to stratify the prognosis of patients with hepatocellular carcinoma (HCC). However, some methodological shortcomings and data interpretation may deserve the authors' attention.

A major conclusion of this study is that the HepatoScore-14 may augment existing staging systems and refine patient prognostic assessment. It should be noted that up to date, at least 10 staging systems have been proposed for HCC.[2] Therefore, to confirm the hypothesis, authors need to first analyze and compare the predictive accuracy of the currently-used staging systems for HCC specifically for the study patients. However, the predictive accuracy, usually expressed by the C-index, was only 0.7 (95% CI: 0.67-0.72) for HepatoScore-14.[1] After combination with the current systems, including BCLC, CTP, CLIP and clinical parameters, the C-index slightly increased to a range of 0.70-0.73, considered not very efficient.[3] Based on these data, it should not be interpretated that the HepatoScore-14 significantly augment the prognostic accuracy of the current systems.

Multiple staging systems for HCC have been proposed and generally claimed to have better prognostic performance. The lack of consensus may result from highly heterogeneous nature of tumor biology and variable treatment strategies at initial staging. In Dr. Morris's cohort, most (n=550) patients were at intermediate stage (BCLC stage C) that could not be treated by the curative methods. This feature makes

the prognostic prediction more complicated since many patients could receive less aggressive or palliative therapy. Furthermore, a confusing point is detected in Table 1 because the total number of patients was not 766 after adding up the numbers in different subgroups (BCLC stage, for example).

In summary, we agree that using a combined set of biomarkers could be a useful approach. However, the clinical significance of integrating this new biomarker into the staging systems is questionable in terms of prognostic performance. More comprehensive evaluation for the existing staging systems should be performed to determine if this new model is indeed a more feasible one in cancer staging.

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