Letter to the Editor

Hepatocellular Carcinoma Intermediate Stage Subclassification Systems: One, None, and One Hundred Thousand

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Dear Editor,

We read with great interest the review by Golfieri et al. [1] recently published in *Liver Cancer*, where various subclassifications of the Barcelona Clinic Liver Cancer (BCLC) intermediate (BCLC B) and advanced (BCLC C) stages of hepatocellular carcinoma (HCC) are examined and discussed in depth. Indeed, the authors conclude that, even though the proposed subclassifications of the various BCLC stages have been tested in the literature with some evidence of improvement in patient prognostication, there is an urgent need for improved staging systems so as to better guide clinicians in the therapeutic choice for HCC and in prediction of the patient's prognosis [2, 3].

The authors in their review emphasize the fact that both the original BCLC staging system – at least as far as the intermediate and advanced stages are concerned – and the various substaging systems that have been published in order to overcome the limitations of the original staging system do not actually fulfil the clinicians' needs in terms of HCC patient prognostication [1]. In untreated patients, we previously demonstrated that the subclassification of the BCLC B stage has prognostic relevance, as the various substages were able to identify contiguous subgroups of patients with statistically significant different survival, and that the substages that we thus identified respected the monotonicity gradient [2]. However, we feel that where the prognostic capability of these systems falls short is when they are tested using a single therapeutic option, as is the case of transcatheter arterial chemoembolization (TACE), which is the only therapeutic option indicated by the original BCLC staging system. Indeed, also studies by Ha et al. [4] and Kim et al. [5] – who proposed further refinement of the BCLC B subclassification – evaluated the prognostic potential of these classification refinements in patients treated with TACE alone [4, 5]. These studies found that the BCLC B subclassification might be further refined either by simply unifying in a single subclass B2 and B3 classes or by modifying the limits of tumoral burden (i.e., “up to 11”) [4, 5]. Indeed, while Ha et al. [4] devised the former solution due to the finding that B2 and B3 patients had similar survivals, Kim et al. [5] hypothesized that pushing the tumoral burden limits to the up-to-11 criterion rather than the original up-to-7 criterion on the basis of some positive evidence provided by the literature on TACE treatment of HCC might nevertheless improve prognostic prediction [4, 5]. Thus, we deemed it of interest to reassess our previously published series of untreated BCLC B HCC patients, reclassifying them according to these 2 proposed subclassification systems [2, 4, 5]. We observed that, using the Ha et al. [4] subclassification, the prognostic capability in our

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Fig. 1. Kaplan-Meier survival curves according to the intermediate stage subclassification proposed by Ha et al. [4].

Fig. 2. Kaplan-Meier survival curves according to the intermediate stage subclassification proposed by Kim et al. [5].

series of untreated patients was not dissimilar to that with the original BCLC B subclassification system, with a progressive and significant ($p < 0.0001$; Fig. 1) decrease in the overall median patient survival from BCLC BI (25 months), BCLC BII (16 months), and BCLC BIII (9 months), although compared to our previous analysis this subclassification did not improve the overall patient prognostication [2, 4]. Moreover, we also tested the subclassification proposed by Kim et al. [5] (Fig. 2) and found that, although also this system identifies significantly different prognostic subclasses ($p < 0.0001$), the 2 intermediate subclasses (i.e., Child-Pugh class A patients outside the up-to-11 criterion [B2A] and Child-Pugh class B patients within the up-to-11 criterion [B2B]) had a strikingly similar overall median survivals (B1: 24 months, B2A: 12 months, B2B: 12 months, and B3: 5 months); therefore, we feel that this finding justifies and confirms the suggestion put forth by the authors of the study to unify the 2 intermediate subclasses (B2A and B2B), once again decreasing the potential of a more subtle discriminatory ability of the proposed subclassification system [2, 5].

All in all, our current results, when analyzed taking into account the reasoning expressed by Golfieri et al. [1] in their review article, further support the notion that the art of prognostication in patients with HCC is not simple or straightforward, and even more difficult is the task of selecting treatment strategies guided by these imperfect staging systems [1, 6]. Thus, we feel that, rather than striving to formulate, or to confirm, the prognostic capability of ever more refined staging and substaging systems, the efforts of clinicians should be aimed at identifying the main drivers of patient prognosis and using them to select the most appropriate therapeutic strategy, following a hierarchical approach to treatment.

Disclosure Statement

None.

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