To predict the future has always been a major concern of humanity. To identify prognostic factors of death and survival is one facet of this concern. A prognostic model is a combination of various factors related to survival in a given disease which allows for the prediction of outcome. Such prognostic models can help to determine the best route for treatment, help to inform patients and their relatives of the prognosis, and to stratify patients in clinical studies. An ideal classification should use simple and easily reproducible clinical variables, clearly sort out patients into several groups with different survival outcomes, and be usable in all populations of patients whatever their origin and the cause of their underlying liver disease. Is there such an ideal classification for hepatocellular carcinoma (HCC)?

HCC almost always occurs in patients with chronic liver disease, usually cirrhosis [1]. Accordingly, survival is strongly influenced by factors related both to tumour extension and liver impairment as well as the occurrence of new tumours. The classifications, including variables only related either to tumour burden or liver function, such as Tumour Node Metastasis (TNM) and Child-Pugh classifications, have obviously insufficient performance in patients with HCC [2,3]. From the first popular classification proposed by Okuda et al. [4] in 1985 to more recent classifications such as BCLC (Barcelona Clinic Liver Cancer) [5], GRETCH (Groupe d’Etude et de Traitement du Carcinome Hépatocellulaire) [6], CLIP (Cancer of Liver Italian Program) [7], CUPI (Chinese University Prognostic Index) [8], and JIS (Japanese Integrated System) [9], all classifications combine parameters reflecting tumour extension (number and size of nodules, vascular invasion, and serum alpha-fetoprotein level) and liver impairment (serum bilirubin, serum albumin, prothrombin activity, ascites, and degree of portal hypertension). Some models also incorporate variables related to patient performance status [5,6]. In this issue of the Journal, Hsu et al. [10] propose a new prognostic model based on total tumour volume calculated by adding up the volumes of all measurable tumours visible on imaging examinations. High total tumour volume was significantly correlated with decreased survival. The best model was the combination of this parameter with Child-Pugh classification and serum alpha-fetoprotein level.

Which is currently the best (ideal) prognostic classification for HCC? There is no consensual answer [11]. However, several clues can help to clarify this topic, coming from recent changes in HCC epidemiology and from clinical studies comparing classifications between them. Due to its great simplicity, Okuda’s score has been widely used for a long time, both in clinical practice and research. However, this score has been built empirically from a population of patients mainly with advanced HCC [4]. The variable reflecting tumour burden (more or less than 50% of total liver volume) is difficult to assess precisely by imaging and is not adapted to the increasing population of patients with small (early) HCC at diagnosis. Recent studies have clearly indicated that Okuda’s score has lower prognostic performance than more recent classifications [6,7,12] and that its use is no longer justified. On the other hand, several studies have found a better performance of the BCLC staging system when compared to other recent classifications [3,12,13]. In the study by Marrero et al. [12] performed in 239 patients with cirrhosis and HCC, BCLC classification had the best predictive power for survival when compared to six other prognostic models (Okuda, TNM, CLIP, GRETCH, CUPI, and JIS classifications). Such a performance is likely due to the fact that it takes into account several important factors such as liver function, portal hypertension, general status, and tumour characteristics with special attention focused on small tumours. The BCLC classification has at least two major advantages. Firstly, it is the most widely accepted classification and the most likely to become the international standard: whatever classification used, it must utilize only one language. Secondly, it is a staging system as well as a prognostic classification, which helps clinicians make more rational decisions for treatment and define proper selection criteria for randomized and non-randomized trials. Accordingly, recent international guidelines recommend the BCLC classification to assess prognosis and to guide decision making process with regards to therapeutic options in patients with HCC [1].

Is this recommendation the end of the story and should we all definitively use the BCLC classification? Have we found the Holy Grail of prognostic models for HCC? The reply is probably negative. As previously emphasized, epidemiological characteristics...
and the treatment of patients with HCC have been markedly modified and hopefully improvements are yet to come. A better identification of patients with chronic liver diseases and cirrhosis would allow to include them in a periodic surveillance program [14]. Recent studies have shown important increases in the rate of patients with small HCC at diagnosis, up to 70% [15]. This fact clearly accounts for currently low performance of prognostic classifications such as Okuda’s score, established a long time ago when patients primarily had advanced HCC at diagnosis. Future classifications will have to identify new, more relevant variables that discriminate between patients with small, early HCC without any vascular or extra-hepatic extension. It is likely that molecular tools, that allow for better characterization of the biological properties of tumours, will be useful for reaching this goal [16]. Moreover, we have to keep in mind that prognostic models generally do not assess spontaneous survival. Due to the high rate of patients with small tumours, many patients receive curative treatment such as surgery or local ablation, [1] and in this latter field particularly, techniques are improving rapidly. Therefore, the therapeutic options suggested by the BCLC staging have to be modified accordingly in the future. Even in patients with advanced tumours, palliative treatments such as arterial chemoembolization [1] or sorafenib [17] are now increasingly used in patients who were receiving only conservative treatments in the past. In addition, a lot of advances have been made in the management of patients with chronic liver diseases and cirrhosis, such as the effective prevention and treatment of varical haemorrhages, but also in antiviral treatment of chronic HCV and HBV infections. These parameters are never taken into account in prognostic studies even if they do modify the outcome of patient survival. Finally, it seems to be clear that a definitive universal prognostic classification for HCC survival does not exist (and likely will never exist). A more realistic way to approach this, is to build specific prognostic models adapted to well-defined subsets of patients that takes into account each therapeutic option. Some models developed in patients with only (or mostly) advanced HCC [18], early-intermediate HCC undergoing non-surgical treatment [19], or resection [20] have been recently published. In patients with small HCC and very well compensated liver disease, it is likely that the usual clinical and biological parameters could be useful for building a prognostic model. More sophisticated variables, based on liver histology or molecular analysis, should be tested [16,21,22]. Such prognostic classifications, specific to each precise situation, will need to be periodically revised in order to follow both future changes in epidemiology, better knowledge of liver carcinogenesis, and improvement of therapy.

Conflicts of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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