Transplant International

INVITED COMMENTARY

Why we need fairer allocation rules for patients with hepatocellular carcinoma awaiting a liver transplant?

Herold J. Metselaar[1], Aad P. van den Berg[2] & Minneke J. Coenraad[3]

1 Division of Hepatology, Department of Hepatology & Gastroenterology, Erasmus University Hospital Rotterdam, Erasmus, MC, The Netherlands
2 Department of Hepatology & Gastroenterology, University Medical Centre Groningen, Groningen, The Netherlands
3 Department of Hepatology & Gastroenterology, Leiden University Medical Centre, Leiden, The Netherlands

Correspondence
Herold J. Metselaar MD, PhD, Division of Hepatology, Department of Hepatology & Gastroenterology, Erasmus University Hospital Rotterdam, Erasmus, MC, The Netherlands.
Tel.:+31 10 7035942;
fax: +31 10 7030352;
e-mail: h.j.metselaar@erasmusmc.nl

Transplant International 2017; 30: 1092–1094

Received: 4 May 2017; Accepted: 5 May 2017

The incidence of both cirrhosis and hepatocellular carcinoma (HCC) is increasing worldwide, despite the current available effective therapy for HCV infection [1]. As liver transplantation is a potential curative option for many patients, the demand for liver transplantation is rising too. Unfortunately, the availability of deceased donor livers has remained stable over the years, leading to a widening of the gap between donor organ supply and demand and a higher waiting list mortality or removal rate. The current waiting list mortality and removal rate within Eurotransplant is, respectively, 18% and 4% [2].

In many European and North American countries, the Model of End-stage Liver Disease score (MELD) forms the basis of prioritization for liver allocation. However, many patients with HCC have a well-preserved liver function, and as a consequence, the MELD score inadequately reflects their risk for dropout from the waiting list from progressive tumour growth. For this reason, exception to laboratory value-based MELD allocation was introduced. HCC patients receive at time of listing additional MELD points, putting them higher on the list and increasing their chance for a timely transplant. Every 3 months, they receive extra points, until they are transplanted or no longer eligible for transplantation [3].

Soon after the introduction of this system, it became clear that this system offered an advantage for HCC

doi:10.1111/tri.12980

patients over non-HCC patients [4]. Moreover, the number of patients with HCC on the waiting list is rising over the last decade, with currently HCC among the most frequent indications for liver transplantation in Europe [5] and the USA [6]. The allocation rule clearly subverts the principle of fairness. Therefore, modifications of the original system have been introduced, including a delay of 6 months before granting additional points, and capping exception points at 34. Unfortunately, this has not sufficiently resolved the disparity between HCC and non-HCC patients. Several alternative HCC-specific scoring systems have been developed to more accurately capture the dropout risk associated with HCC progression and with the severity of liver disease as represented by MELD [7]. In this issue, two HCC-specific systems, namely MELD equivalent ($MELD_{EQ}$) and dropout equivalent MELD (deMELD), are subjected to an extensive analysis of recent United Network for Organ Sharing (UNOS) data [8].

Both $MELD_{EQ}$ and deMELD incorporate tumour-specific parameters (tumour size and number, AFP) and the laboratory MELD. The main differences between the two scores are that the $MELD_{EQ}$ assigns extra points after 6 months on the waitlist and deMELD gives greater weight to tumour size and laboratory MELD.

Do both systems correct the current inequity in transplantation and dropout between non-HCC and HCC patients? To a certain degree, the answer is yes. $MELD_{EQ}$ and deMELD predicted dropout rate better (C-indices of 0.678 and 0.664, respectively) as compared with the currently used HCC exception score (C-index of 0.568), but they still fall short when compared with the labMELD for non-HCC patients dropout prediction (C-index of 0.832). Both scores match actual dropout probabilities comparably to non-HCC groups with labMELD scores < 22, but fail in non-HCC groups with labMELD scores ≥ 22.

Another concern with these HCC-specific scores is the less favourable outcome after transplantation in patients with equivalent MELD scores between 22 and 30, suggesting that these scores prioritize patients with biologically more aggressive tumours. This should be clarified in future studies, as transplant benefit and utility are in our view very important, considering the scarcity of donor organs.

Where does this bring us? It is clear that these HCC-specific MELD adaptations may to a certain extent improve equitability in access to liver transplantation between HCC and non-HCC patients, but they are certainly not the final solution. What we need is a combination of predicted risk of wait list mortality and dropout and (disease-free) survival after transplantation to further optimize the use of scarce donor organs while providing equal access for all patients on the waiting list for liver transplantation. The introduction of any HCC-specific MELD system would need very close assessment to make sure that they are accomplishing the predefined goals of allocation systems, namely equity, transplant benefit, transparency and accountability [9]. It is foreseen that fine-tuning of HCC-specific scores is needed to accomplish these goals. Tumour characteristics such as AFP level, histologic differentiation grade, microvascular invasion and response to loco-regional treatment may be of help to predict biological behaviour of HCC.

Another obvious way to tackle this conundrum is to increase the availability of donor organs. Apart from living donor liver transplantation, machine preservation will hopefully increase deceased donor supply in the near future.

Funding

The authors have declared no funding.

Conflicts of interest

The authors have declared no conflicts of interest.

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