Review Article

Transplantation for hepatocellular cancer: pushing to the limits?

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Abstract: Milan criteria (MC) represents the cornerstone in the selection of patients with hepatocellular cancer (HCC) waiting for liver transplantation (LT). MC represent the precursor of the scores based on the idea of "utility": in other terms, the scoring systems typically used in the field of LT oncology present the exclusive aim of selecting the cases with the best post-LT outcomes. However, some other scores have been proposed specifically investigating the risk of death or tumour progression during the waiting list. In this case, the selection process is connected with the idea of "priority": patients at higher risk for drop-out (DO) should be selected, prioritising them or, conversely, deciding to de-list them due to the high risk of post-LT futile transplant. Lastly, models based on the concept of "benefit", namely the balancing between priority and utility, have been recently created. The present review aims to examine these three different types of scoring systems, trying to underline their pro and cons in the allocation process of HCC patients.

Keywords: Milan criteria (MC); recurrence; drop-out (DO); benefit

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Introduction

Milan criteria (MC) represents the cornerstone in the selection of patients with hepatocellular cancer (HCC) waiting for liver transplantation (LT) (1). After their introduction in 1996, several new scoring systems have been proposed with the intent to push beyond the patient selection limits (2). In fact, although the MC consent to obtain excellent post-LT survival rates, they are very restrictive, thus impeding to transplant a significant number of subjects having border-line tumoral conditions.

However, when we need to identify the best selection model to use for selecting HCC patients, typically we think at a score contemporaneously able to improve the number of transplantable cases and to maintain a low rate of HCC-specific death or recurrence (3). Such a scheme, typically used for constructing the vast majority of the proposed West and East scoring systems, is substantially based on the idea of "utility" (4-8).

However, some other scores have been proposed specifically investigating the risk of death or tumour progression during the waiting list (drop-out, DO) (9-11). In this case, the selection process is connected with the idea of "priority": patients at higher risk for DO should be selected, prioritising them or, conversely, deciding to de-list them due to the high risk of post-LT futile transplant.

Lastly, models based on the concept of benefit have been recently created (12-15). The transplant benefit represents a compromise between utility and priority, trying to define the group of patients better really obtaining a beneficial effect concerning survival after LT (16).

The present review aims to examine these three different types of scoring systems, trying to underline their pro and cons in the allocation process of HCC patients.

Utility models: from the dictature of morphology to the realm of biology

In 1996, Mazzaferro *et al.* proposed the so-called MC, constructing a model based on the combination of number and dimension of the tumoral burden (1). Afterwards, several new morphology-based scores were proposed, all of them trying to slightly enlarge the number of potentially transplantable patients without contemporaneously decreasing the remarkable survivals obtained using the MC (*Table 1*) (2,4,6-8). In 2009, Mazzaferro *et al.* proposed a new model derived from the sum of number and dimensions of a tumour: the up-to-seven criteria (5), However, in the same period, growing evidence started raising on the opportunity to combine morphological and biological elements, with the main intent to improve the patient selection. In 2010, an Editorial by Marsh *et al.* interestingly stated that: "… in the field of surgical oncology, tumour biology is king, patient selection is queen, and technical manoeuvres are the prince and princess who try, but usually fail, to usurp the throne." Among the different biology-related variables, alpha-fetoprotein (AFP) was the most commonly analysed feature (17-23,28,35). Its absolute value available immediately before the transplant was correlated with a higher risk for post-LT recurrence (35). Its slope was similarly connected with an improved ability in selecting the risk for recurrence or intention-to-treat (ITT) death, even if they were within the MC (17,28). Several cut-offs were tested, with the most commonly proposed ones being 400 or 1,000 ng/mL (18-20). Studies exploring the combination of AFP with other radiological and biological aspects were proposed (17-23). As an example, three scoring systems investigating the integration between radiological aspects and AFP were recently proposed and validated (21-23). Another biological marker analysed in combination with AFP or alone was the des-gamma-carboxy prothrombin (DCP) (24,25,36). A recent study from Korea has shown that the combination of DCP and AFP consented to improve the prognostic ability in living-donor LT subjects (25). A meta-analysis confirmed the prognostic role of DCP, with a 5-fold increased risk of recurrence after LT (36).

The role of inflammatory markers has also been investigated in the specific field of LT. As an example, the neutrophil-to-lymphocyte ratio has been evaluated as a single prognostic tool or after its integration with other variables, showing great ability in the prediction of ITT survival and post-LT recurrence (21,22,29,30). Similarly, the platelet-to-lymphocyte ratio has shown a good prognostic ability in a recent meta-analysis, reporting a 3-fold increased risk for recurrence in patients having high values of this ratio (37).

The radiological response to loco-regional treatments has been similarly investigated. Progression disease has been proposed as an important selection tool in recent studies coming from Europe, Asia and the US (17,21,38,39). Studies from Asia and Europe also investigated the uptake of the F-18 fluorodeoxyglucose (FDG) after positron emission tomography (PET), combining this element with the radiological aspects of the tumour (26,27,31).

Some studies proposed to perform a pre-LT biopsy with the intent to select the patients according to the histological features of the tumor (32-34). Among them, a study from Padua underlined the importance of the tumor grading, showing that transplanting patients with well-to-moderated grading even exceeding the MC was connected with acceptable survivals (32).

A study from the US identified the fractional allelic imbalance rate index as an important discriminating tool for selecting patients at high risk for HCC recurrence after transplant. The fractional allelic imbalance was found to be the strongest predictor of recurrence, followed by vascular invasion, tumor number, and hepatic lobar involvement (33).

The recently proposed Toronto criteria were based on three aspects: (I) no vascular invasion detected at imaging; (II) tumor exclusively located into the liver; and (III) no poor grading on biopsy. Comparing the results of 189 MC-IN *vs.* 105 Toronto criteria patients, no differences were observed in terms of 5-year overall (72% *vs.* 70%) and disease-free survivals (70% *vs.* 66%) (34).

Lastly, we should like to underline that several of the studies reported in this session mainly focused on the combination of different features (morphological + biological or biological + biological), thus proposing the idea that the different risk factors for recurrence or death may cause a cumulative effect (6,7,9,15,17-27).

Priority models: finding a model for equalizing the MELD score

The Model for End-stage Liver Disease (MELD) represents the best tool for selecting no-HCC patients waiting for LT. However, when we try to find a similar score able to select and prioritise patients having a tumour, we have the significant problem of trying to "equalise" these two different groups of patients. In fact, the main risk in this setting is to violate the rule of "equity": in other terms, we

Table 1 "Utility" scoring systems. Three subgroups of morphology-only, combined morphology-biology, and biology-only scoring systems have been shown

Author (Ref.)	Score name	Year	Country	Variables of the score
Only morphology				
Mazzaferro (1)	Milan	1996	Italy	1 HCC ≤5 cm or 2–3 HCC ≤3 cm
Yao (4)	UCSF	2001	USA	1 HCC ≤6.5 cm or 2–3 HCC ≤4.5 cm with TTD ≤8 cm
Mazzaferro (5)	Up-to-seven	2009	Europe	Number + maximum size of HCC =7
Lee (8)	Asan	2008	Korea	1–6 HCC ≤5 cm
Combined radiology and biology				
Ito (6)	Kyoto	2007	Japan	1–10 HCC ≤5 cm and DCP ≤400 mAU/mL
Zheng (7)	Hangzhou	2008	China	TTD ≤8 cm or HCC grading I or II and AFP ≤400 ng/mL
Lai (17)	EurHeCaLT	2013	Europe	mRECIST progression disease or AFP slope ≥15.0 ng/mL/month
Toso (18)	TTV/AFP	2009	Switzerland, USA	TTV ≤115 cm^3 and AFP ≤400 ng/mL
Lai (19)	TTD/AFP	2012	Italy	TTD ≤8 cm and AFP ≤400 ng/mL
Duvoux (20)	AFP score	–	France	Largest tumor size: ≤3 cm =0; 3–6 cm =1; >6 cm =4
				Tumor number: 1–3 = 0; ≥4 = 2
				AFP: ≤100 ng/mL =0; 100–1,000 ng/mL =2; >1,000 ng/mL =3
				Cut-off >2
Lai (21)	TRAIN	2016	Belgium, Italy	0.988 (if mRECIST progression disease) +0.838 (if AFP slope ≥15.0 ng/mL/month) +0.452 (if NLR ≥5.0) –0.03*waiting time months
				Cut-off ≥1.0
Halazun (22)	MORAL	2017	USA	Pre-MORAL: preoperative NLR ≥5=6; maximum AFP >200 ng/mL =4; largest tumor size >3 cm =3
				Post-MORAL: grade 4 tumor =6; vascular invasion =2; argest size on path >3 cm =3; tumor number on path >3=2
				0–2= low; 3–6= medium; 7–10= high; >10= very high risk
Mazzaferro (23)	Metroticket 2.0	2018	Italy China	AFP <200 ng/mL and number + maximum size =7
				AFP 200–400 ng/mL and number + maximum size ≤5
				AFP 400–1,000 ng/mL and number + maximum size ≤4
Taketomi (24)	Kyushu Fukuoka	2009	Japan	Tumor size <5 cm or DCP <300 mAU/mL
Lee (25)	MORAL	2016	Korea	11*√DCP + 2*√AFP; cut-off > 314.8
Hsu (26)	UCSF/PET	2016	Taiwan	Low-risk: UCSF-IN and FDG-PET negative
				Intermediate-risk: UCSF-OUT and FDG-negative; or FDG-positive and TNR <2
				High-risk: FDG-positive and TNR ≥2
Kornberg (27)	Munich	2012	Germany	PET positive; AFP ≥400 ng/mL; TTD ≥10 cm

Tbale 1 (*continued*)

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Author (Ref.)	Score name	Year	Country	Variables of the score
Only biology				
Vibert (28)	AFP slope	2010	France	AFP slope ≥15.0 ng/mL/month
Halazun (29)	NLR	2009	USA	NLR (< versus ≥5)
Lai (30)	NLR/PLR	2014	Belgium	NLR (< versus ≥5) and PLR (<150 versus ≥150)
Hong (31)	AFP/PET	2016	Korea	High risk: AFP level ≥200 ng/mL and PET positive
Cillo (32)	Grading	2004	Italy	Well/moderate grading
Dvorchik (33)	FAI	2008	USA	Fractional allelic imbalance
DuBay (34)	Totonto	2016	Canada	No vascular invasion at imaging; HCC confined to the liver; no poor differentiation on biopsy

HCC, hepatocellular cancer; UCSF, University of California San Francisco; TTD, total tumor diameter; DCP, des-gamma carboxy-prothrombin; EurHeCaLT, European Hepatocellular Cancer Liver Transplantation; AFP, alpha-fetoprotein; mRECIST, modified Response Evaluation Criteria in Solid Tumors; TTV, total tumor volume; TRAIN, time-radiological response-alpha-fetoprotein-inflammation; NLR, neutrophil-to-lymphocyte ratio; MORAL, model of recurrence after liver transplant; PET, positron emission tomography; TNR, tumor to nontumor ratio; FDG, fluorodeoxyglucose; PLR, platelet-to-lymphocyte ratio; FAI, fractional allelic imbalance.

favour a specific subclass, harming the other one regarding increased risk of DO.

In the US, the policy of adding MELD exception points for HCC individuals represents the typical strategy. However, several modifications have been done during the years, with the intent to reduce possible unbalances (40,41) (*Table 2*).

A first attempt to create a score able to consent an equitable liver allocation process was proposed in 2006: the HCC-MELD score was developed, showing that the factors associated with the risk of removal for HCC are different from non-tumour candidates (42). A statistical refinement of the score was performed some years later, performing a competing-risk analysis for the identification of the independent risk factors for de-listing: MELD and AFP value confirmed their important role in this setting (43).

In 2012, a large study from the US proposed the DO equivalent MELD (deMELD). This model was able to assess the risk of DO in patients with or without HCC, trying to find a better comparison of the opportunities of these patients of being transplanted. Unfortunately, the main limit of the present score is its complexity based on several tumour- and patient-related covariates (9).

Another study proposed the MELDEQ, in which the MELD points were combined with AFP, tumour number and tumour dimensions (10).

A study from Quebec, Canada, implemented the MELD model adding points according to several combinations of tumour diameters and nodules numbers: using this model, the transplant rates among HCC and no-HCC cases became equivalent, without compromising post-LT graft and patient survival (11).

A recent study coming from Cleveland (US), interestingly showed that the use of a continuous risk score able to longitudinally assess the risk for DO and ITT death was superior respect to dichotomous variables in determining a more granular estimation of the risk: also, in this case, MELD and tumour-related variables were integrated (45).

Although several aspects have been deeply investigated, some significant variables, like the different blood groups, have not been exhaustively indagated in terms of ability to modify the waiting time/demand for LT in the field of HCC (46). More studies are needed on this specific aspect.

Benefit models: a challenging balancing

The concept of transplant benefit expresses the survival gain obtained comparing LT with the best alternative therapies (i.e., a difference between life years obtained with and without LT). The transplant benefit used with a mid-term time horizon (post-transplant 5–10 years) has the inherent potential to reach the dignity of an independent LT selection principle (3).

In 2008, Volk *et al.* first investigated this concept, looking at the comparison between the survival benefit of transplanting an HCC patient exceeding the MC, versus the

Table 2 "Priority" and "Benefit" scoring systems

Author (Ref.)	Score name	Year	Country	Variables of the score
"Priority" scores				
Freeman (42)	HCC-MELD	2006	USA	1–0.920 exp[0.09369 (MELD at listing –12.48)+0.00193 (AFP–97.4) +0.1505 (maximum tumor size –2.59)
Washburn (43)	HCC-MELD competing-risk	2010	USA	Refinement of the previous HCC-MELD score based on MELD and AFP value
Toso (9)	deMELD	2012	USA	–25 +0.1*Age +1.6*MELD +1.6*tumor size +1.3*LogAFP +6.0 if nodules ≥2+0 (if HCV) –1 (if HBV) +3 (if alcohol) +3 (if NASH) +1 (if hemocromatosis) +1 (if other)
Marvin (10)	MELDEQ	2015	USA	1.143*MELD +1.324*LogAFP +1.438*number of nodules +1.194*max Tumor size + c(t) c(t) = –2/0.146 if t <6 months; c(t) = –1/0.146 if t ≥6 months
Bhat (11)	Quebec HCC MELD	2017	Canada	25 points: 1 lesion 4.1–5.0 cm; 3 lesions, all 2.1–3.0 cm; 3 lesions, 2 of whom 2.1–3.0 cm and 1 lesion ≤2.0 cm
				22 points: 1 lesion 3.1–4.0 cm; 2 lesions, all 2.1–3.0 cm; 3 lesions, 1 of whom 2.1–3.0 cm and 2 lesions ≤2.0 cm; 3 lesions, all ≤2.0 cm
				20 points: 2 lesions, 1 lesion 2.1–3.0 cm and 1 lesion of lesser diameter
				18 points: 2 lesions both ≤2.0 cm
				16 points: 1 lesion 2.1–3.0 cm
				Biological MELD: 1 lesion ≤2.0 cm
"Benefit" scores				
Vitale (12)	HCC-MELD	2014	Italy	1.27*MELD –0.51*logAFP +4.59
Lai (15)	ITT transplant benefit	2017	Europe	Risk factors: AFP ≥1,000 ng/mL, mRECIST progression disease, mRECIST complete response and MELD ≤13
				No negative factors = large benefit (60 months median benefit)
				1 negative factor = moderate benefit (40 months median benefit)
				2 negative factors = small benefit (20 months median benefit)
				3–4 negative factors = no benefit (0 months median benefit)
Cillo (44)	ISO score	2015	Europe	HCC with downstaging or partial response: HCC-MELD + extra points for time
				MELD 22 at entry + extra points for time
				HCC first presentation or late recurrence: HCC-MELD
				HCC complete response or T1: biochemical MELD

HCC, hepatocellular cancer; MELD, model for end-stage liver disease; AFP, alpha-fetoprotein; deMELD, drop-out equivalent MELD; HCV, hepatitis C virus; HBV, hepatitis B virus; NASH, non-alcoholic steato-hepatitis; MELDEQ, MELD-equivalent; HALT, Hazard associated with liver transplantation for hepatocellular carcinoma; TBS, tumor burden score; MELD-NA, model for end-stage liver disease-sodium; ITT, intention-to-treat; mRECIST, modified Response Evaluation Criteria in Solid Tumors.

harm caused in no transplanting no-HCC patients on the waiting list. Interestingly, the harm outweighed the benefit of transplantation when the post-LT 5-year survival for HCC cases was <61%, with a threshold ranging 25–72% according to the different donation numerosity observed in the different areas (37).

Similar evidence was shown in a similar study performed in Italy, in which the high number of donors in the region determined a relatively low 5-year survival rate (only 30%) for consenting the transplant benefit to outweigh the harm (47).

Another study from Italy explored a large population of HCC patients with the intent to explore the transplant benefit

in different subgroups according to the Barcelona Clinic Liver Cancer (BCLC) class. The median 5-year transplant benefit was 11.2 months for BCLC 0, 13.5 for BCLC A, 17.4 for BCLC B-C, and 28.5 for BCLC D, thus showing a growing benefit with the growing severity of liver dysfunction (48). Two recent "benefit-related" scores have been proposed (*Table 2*).

A study based on 2,697 enlisted and 1,702 transplanted subjects consented to develop the HCC-MELD score. The score consented to calculate a numerical score for HCC patients based on the combination of AFP and MELD, whereby consenting to obtain a transplant benefit equal to that of no-HCC patients with the same numerical value for MELD (12).

A multicentric European study performed on 2,103 HCC patients introduced the new concept of ITT transplant benefit, being able to estimate the benefit from the moment of waiting list inscription. Four risk factors for the development of a significant benefit were defined, namely AFP ≥1,000 ng/mL, mRECIST progression disease, mRECIST complete response e MELD ≤13. After using the combination of these four variables, it was possible to identify four groups of patients presenting large to no benefit (15). A recent score developed in Italy, the so-called "ISO Score" has been proposed with the intent to modify the liver allocation policy. A "mixed" approach has been proposed, in which the indicators for orienting organ allocation policies based on the principles of urgency, utility, and transplant benefit have been identified. MELD exceptions and HCC have been analyzed to construct a LT priority algorithm aimed at overpassing the inequity of a purely MELD-based system (44).

Considerations and conclusions

The decision to use a specific scoring system in selecting HCC patients deserving LT presents several challenging decisions to take. The first consideration to do is connected with the model to construct. A score must be easy to be used, but contemporaneously able to consent good discrimination. This exigence limits the possibility to use sophisticated models requiring several variables. All the reported scores typically use the same, limited, number of variables. MELD score is typically present in "priority" scores, being integrated with some tumour-related variables (i.e., AFP, tumour response, tumour morphology). For the "utility" scores, number and dimension of a tumour combined with some biological aspect (AFP or radiological response) represent the easier way of capturing the risks of recurrence or HCC-specific death. Typically, the cumulative effect of the different risk factors improves the prognostic ability of the model, as shown in different experiences (6,7,9,15,17-27).

For the "benefit" scores, as expected, a combination of "utility" and "priority" elements has been adequately reported (i.e., MELD, AFP, radiological response).

Another critical consideration is strictly connected with ethical issues. Which one of these selection scores should be preferred? As reported, the benefit represents the balancing between priority and utility. As a consequence, it should adequately represent the best way of constructing models based on the principle of equity, thus consenting to give the same opportunities to HCC and no-HCC patients. Unfortunately, the complexity of a waiting-list population is difficult to be easily captured by a user-friendly score. We retain a sort of compromise should be attempted, creating two different models. An easy-to-use "priority" score based on the combination of HCC-related features and MELD should be developed, aimed at selecting in an equal way tumour and non-tumour patients waiting in the list. Then, a similar "utility" score aimed at identifying patients at risk for HCC-specific death should be proposed, with the possible double intent of (I) excluding patients at high future risk of recurrence (futile transplant), or (II) following-up with greater attention identified high-risk cases after transplant.

Lastly, we should like to stress another important issue directly connected with the concepts of "inclusion" and "exclusion" from the LT. If, on one side, the exclusion of patients with a "too advanced" tumor looks to be intuitive, on the other the decision to treat with alternative approaches a patient with a tumor at very low risk for progression or recurrence represents a big deal. As an example, patients showing a complete biological/radiological response and a low MELD should remain for a long period in the waiting list presenting a very low risk for DO (15,49). Consequently, these patients may be de-listed and strictly followed-up for the risk of recurrence. However, all of the here reported issues require further studies with the intent to find the best way of equilibrating the severe imbalance existent in the allocation process of HCC patients.

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Footnote

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