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SUPPLEMENT

Milan Criteria in Liver Transplantation for Hepatocellular Carcinoma: An Evidence-Based Analysis of 15 Years of Experience

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Hepatocellular carcinoma (HCC) is the seventh most common cancer worldwide and the third most common cause of cancer-related deaths; the number of new cases per year is approaching 750,000.[1]

The magnitude of the incidence of HCC has discouraged any attempts to apply liver transplantation (LT) as the prevailing curative therapy for HCC worldwide because of the limited sources of donated organs (deceased and living donors) and the poor access to sophisticated health care systems in some geographical areas. If these limitations continue to prevail throughout the world, any attempt to significantly reduce HCC-related mortality rates through the application of LT will be delusional.

International experiences have confirmed, however, the potential of LT to definitively cure HCC because it presents a unique opportunity to remove both the tumor (HCC is associated with 695,000 deaths per year[1]) and the underlying cirrhosis. Despite its limited access, LT has become the standard of care for patients with small HCCs and the main driving force for alternative strategies offered to patients with intermediate HCCs.

In 1996, a prospective cohort study defined restrictive selection criteria that led to superior survival for transplant patients in comparison with any other previous experience with transplantation or other options for HCC.[2] Since then, these selection criteria have become universally known as the Milan criteria (MC) in recognition of their origin. Ever since their adoption in clinical practice, the MC have helped doctors to single out early-stage HCC as a prognostic category of cancer presentation that is amenable to curative treatments. After their implementation, the favorable posttransplant outcomes that were observed in cohort series were so convincing that the MC immediately became the standard of care for early HCC, and further validation by randomized controlled trials (RCTs) was prevented.

After the passage of approximately a decade, researchers began to challenge the MC with other proposals designed to capture those patients not meeting the MC who could achieve similar posttransplant survival rates through the expansion of the accepted tumor limits for transplant eligibility.

None of these expanded criteria have become the new reference standard for selecting LT candidates with HCC; any broadening of the selection criteria for transplantation is inevitably hampered by severe

Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; df, degrees of freedom; HCC, hepatocellular carcinoma; LT, liver transplantation; MC, Milan criteria; MELD, Model for End-Stage Liver Disease; mVI, microvascular invasion; NA, not applicable; n/n, number of studies/number of patients; NOS, Newcastle-Ottawa scale; RCT, randomized controlled trial; TACE, transarterial chemoembolization.

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TABLE 1. Inclusion and Exclusion Criteria for the Literature Search

Variable	Inclusion Criteria	Exclusion Criteria
Population type	Human LT for cancer (HCC)	Nonhumans Nonliver transplantation Not HCC with cirrhosis
Intervention	Within the MC or beyond the MC (for comparisons with patients within the MC)	Beyond the MC only Extended criteria only
Outcome	Survival (overall, disease-free, and recurrence-free)	Data not available

restrictions in donor availability. Consequently, the MC remain the benchmark for any transplant strategy involving patients with HCC and the cornerstone for decision making for other patients at any stage.

Surprisingly, no systematic review of the available experiences with the MC has been published yet; the suboptimal quality of the literature and the poor application of evidence-based principles has prevented this exercise. The aim of this study was to fill the gap through a systematic review of the available evidence on the MC and the related issue of the position of LT in the treatment algorithm for HCC.

MATERIALS AND METHODS

Definition and Endpoints

For the literature review, analysis, and discussion, the MC were defined as follows: a single HCC nodule with a maximum size of 5 cm or as many as 3 nodules with the largest not exceeding 3 cm and no macrovascular invasion.[2]

The systematic analysis was tailored to 2 predetermined questions:

1. Is the posttransplant survival of patients influenced by the MC when they are assessed at the time of the explant pathology examination?
2. Do the boundaries of the MC correlate with a reduced likelihood of detecting 2 pathology surrogates of tumor behavior: microvascular invasion (mVI) and poor differentiation (grade 3)?

In addition, we also probed the literature to answer less stringent questions (eg, the role of pretransplant treatments in patients meeting or not meeting the MC at the time of wait listing).

Review Methodology

A review of the literature in English was performed with various search terms. A PubMed-, Embase-, and Scopus-based search strategy was used that combined text, keywords, and Medical Subject Headings terms for titles and abstracts. Manual cross-referencing was also used to find more relevant articles. This part of the search strategy was not restricted by date. The following search terms were used in various combinations: *Milan criteria*, *primary liver cancer*, *primary liver tumor*, *hepatoma*, *hepatocellular carcinoma*, *HCC*, *BCLC A*, *T1-T2*, *tumor size*, *tumor number*, *tumor burden*, *metastatic disease and metastases of HCC*, *transplantation*, *liver transplantation*, *liver substitution*, *orthotopic liver transplantation*, *OLT*, *LT*, *living donor liver transplantation*, *deceased donor liver transplantation*, *survival*, *overall survival*, *recurrence-free survival*, *RFS*, *disease-free survival*, *DFS*, *prognosis*, *death*, *recurrence*, *tumor relapse*, *time to recurrence*, *time to relapse*, and *TTR*.

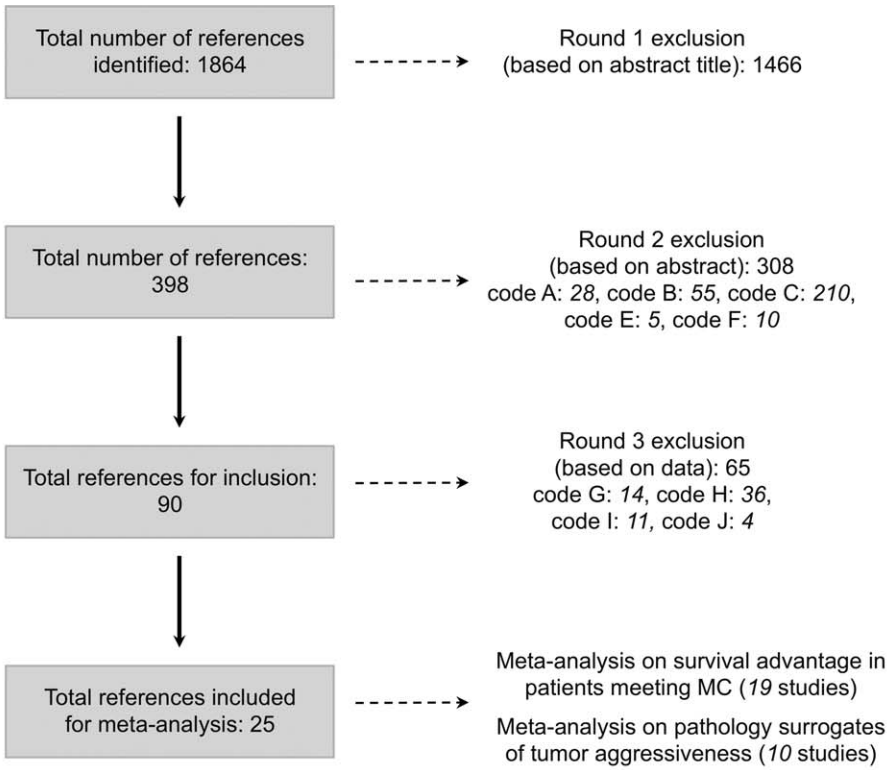
Because of the large quantity of reports including the use of the MC in the setting of HCC management, case studies and reviews that were not focused specifically on the MC were not considered. Abstracts were selected according to the inclusion-exclusion criteria and the review methodology, which are outlined in Table 1 and Fig. 1, whereas studies lacking explant pathology data (which were used to check for adherence to the MC) were not entered into the meta-analysis (exclusion code G).

Ranking Criteria and Meta-Analysis of Pooled Data

The classification proposed by the Oxford Centre for Evidence-Based Medicine was used to rank each publication in the particular subset of prognosis-oriented studies.[3,4] This methodology, in combination with a quality assessment scale for case-control and cohort studies proposed by the Newcastle-Ottawa group [ie, the Newcastle-Ottawa scale (NOS)],[5] allowed a comprehensive review of the current evidence.

The ranking of the studies and the assumptions were made specifically in terms of prognosis according to practice and the literature search; for this purpose, the MC were considered a prognostic covariate rather than a therapeutic covariate. Accordingly, in the Oxford Centre for Evidence-Based Medicine scheme, specific grading criteria for assigning levels of evidence are used to discriminate prognosis-oriented studies from therapy-oriented studies; the latter consist of systematic reviews of RCTs (including meta-analyses), whereas the former include case-control and cohort studies.[3-5]

The allocation of each study to the predefined categories was independently performed by 2 reviewers who were trained in the field of transplantation and HCC. All cases of possible inconsistencies between the reviewers were discussed so a shared judgment of the study's final allocation could be reached.



Exclusion Code	Rationale
A	Not HCC only
B	Not LTor LT beyond MC only
C	Editorials, letters, abstracts missing series description, reviews or clinical studies missing specific focus on MC or lacking any reference to MC in the discussion of LT for HCC
E	Nonhuman
F	Non-English
G	No explant pathology available
H	No direct comparison between MC patients and patients beyond MC for the evaluated parameters
I	No complete data for statistical analysis of survival or pathology surrogates (vascular invasion, tumor grading, microsatellites)
J	Survival analysis based only on intention-to-treat analysis missing explant pathology data

Figure 1. Review methodology.

The studies were selected and then ranked with the Oxford Centre for Evidence-Based Medicine classification and the NOS quality assessment; hazard ratio estimates, which were extracted from sufficiently powered individual studies, were combined for the meta-analysis with the generic inverse variance method according to a random effect model. Meta-analysis techniques were also used for aggregating frequency data for the distribution of pathology surrogates (ie, mVI and tumor grading) across individual studies. For this analysis, the Mantel-Haenszel random effect method was applied, and the odds ratio was the investigated association measure. Presuming an excess of variability (heterogeneity) in the study results, we used the random effect models to produce more conservative estimates of the significance of treatment effects in comparison with estimates from fixed effect models.

Calculations were performed with RevMan 5 (Cochrane Information Management System, Copenhagen, Denmark).[6]

P values below the conventional 5% threshold were considered statistically significant.

TABLE 2. Stratification of Selected Studies According to the Levels of Evidence and the Quality Assessment

Level of Evidence According to Prognosis*	Sample Size and Quality Assessment†		Recommendation Grade
	Studies/Patients (n/n)	NOS Rank Average (Range)	
1a	Systematic review with homogeneity of inception cohort studies and clinical decision rules validated in different populations		A
	0/0	—	
1b[2,10–23]	Individual inception cohort study with >80% follow-up or clinical decision rules validated in a single population		A
	15/1612	7 (6-8)	
1c	All-or-none case series		B
	0/0	—	
2a[24–26]	Systematic review with homogeneity of either retrospective cohort studies or untreated control groups in RCTs		B
	3/8201	7 (6-8)	
2b[27–88]	Retrospective cohort study or follow-up of untreated control patients in an RCT or derivation of clinical decision rules validated in a split sample only		B
	62/7842	6 (4-8)	
2c	Outcomes research		C
	0/0	—	
3a	Systematic review of case-control studies		C
	NA	—	
3b	Individual case-control study		C
	NA	—	
4[89–92]	Case series (and poor-quality prognostic cohort studies)		C
	4/125	5 (3-6)	
5[93–98]	Expert opinion without an explicit critical appraisal, bench research, or first principles		D
	6/NA	NA	

NOTE: n/n: number of studies/number of patients. NA: not available. Clinical decision rules consist of algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category. In the Oxford Centre for Evidence-Based Medicine guidelines, level 3 studies (systematic reviews of case-control studies or individual case-control studies) do not apply to prognosis-oriented analyses because these are consistent with the consideration of the MC as a prognostic category rather than a diagnostic or therapeutic category.

*According to the Oxford Centre for Evidence-Based Medicine categorization of prognosis.[4]

†According to the NOS for case-control and cohort studies.[5]

RESULTS AND DISCUSSION

The first Web search resulted in a total of 1864 references; 1466 references were discarded as irrelevant because of the abstract title. Another 308 references were discarded because they did not comply with a predefined list of inclusion and exclusion criteria, which are outlined in Table 1 and Fig. 1.

Therefore, 90 references were included in the final review. There were 2 main subclasses:

1. Studies describing LT outcomes with respect to the MC or using the MC as the reference standard for intraseries comparisons (n = 48).
2. More heterogeneous studies describing the MC as a major determinant for the prognosis of patients with HCC undergoing LT (deceased donor LT, living donor LT, salvage transplantation, or pediatric transplantation) versus patients undergoing resection or other combined therapies (n = 42).

In order to generate the meta-analysis, another cut to 25 references was necessary; 65 of the 90 studies were discarded according to exclusion codes G to J (Fig. 1).

The stratification of the studies with a prognosis-oriented analysis revealed that 65 of the 90 studies (72%) reached an intermediate level of evidence (grade 2); only 17% of the studies were solid enough for grade 1b evidence, and the remaining studies were positioned at suboptimal levels (grades 4 and 5). In general, there was a significant correlation between the Oxford Centre for Evidence-Based Medicine level of evidence and the NOS-determined quality of the studies, even after quality adjustments were made to avoid overestimations of non-RCTs[7-9] (for a summary of the stratification of the studies, see Table 2).

The 90 studies, which spanned 15 years,[2,10-98] included 17,780 patients; only 1612 patients qualified for level 1b studies, and 16,043 qualified for level 2 studies. Presumably, this sample size represented

less than 10% of the total number of patients who underwent transplantation for HCC and a negligible fraction of the potential transplant candidates with HCC who were observed during the same period. An unavoidable overestimation of the exact number of patients collected by the data pooling may have occurred because of the possible overlapping effect of patients recruited to multicenter studies. However, the aforementioned assumptions are confirmed by the estimated number of potential candidates with HCC who could benefit from LT, that is, more than 20,000 per year in the United States alone; this number far exceeds the number of deceased donors per year in the United States (8000).

Having established the limits of the representativeness of the sampling and the suboptimal level of the evidence, we present the results, which are ordered in accordance with the predetermined endpoints, in the following sections.

Does the Application of the MC to Patients With Cirrhosis and HCC Improve Patient Survival After LT?

MC and Nontumor Indications

The current widespread acceptance of LT candidacy via the MC indicates the general acceptance of the reliability of these criteria in comparison with the pioneering days when the MC were not in place and LT for HCC was considered barely palliative.[99]

Indeed, in 9 studies, patients with chronic hepatitis and cirrhosis who met the MC and underwent LT for HCC achieved posttransplant survival rates comparable to those of patients with nontumor indications for LT. Although they were not designed to specifically address a survival equivalence between LT patients within the MC and LT patients with nontumor indications, 4 prospective cohort studies (level 1b)[2,10,11,13] and 5 retrospective cohort studies[29,32,39,45,46] (level 2b) reported 5-year survival rates of 65% to 78% for patients meeting the MC and 68% to 87% for patients with nontumor indications. The European Liver Transplant Registry, the Organ Procurement and Transplantation Network, and the Australian and New Zealand Liver Transplant Registry[100-102] have confirmed survival rates of 70% to 82% for patients with nontumor indications. Incidentally, these studies did not compare patients within the MC who were treated with transplantation and patients to whom nontransplant therapies were offered. However, other noncomparative studies have reported that the 5-year survival rates of HCC patients have improved with time, and these improvements started with the implementation of the MC in the clinical practice.[103]

MC and Transplantation for Patients With HCC Beyond Conventional Indications

Since the path of LT for HCC was reopened in 1996, a few prospective studies and several retrospective cohort studies based on intraseries comparisons (ie, lacking external validation) have shown significant improvements in the survival rates of patients undergoing LT for HCC within the MC versus patients with HCC beyond the MC (level of evidence 2b).

An analysis of the results of LT for patients exceeding the MC is beyond the scope of the present review because any comparisons with extended criteria are biased by the fact that no prospective studies or RCTs of indications for LT for HCC beyond the MC have ever been conducted. However, the significant deterioration in survival that is observed when the MC limits are exceeded should be outlined; the 5-year survival rates of these patients are as low as 46% to 60%.

The meta-analysis included 19 studies[2,15,16,19,26,33,35,39,40,42,46,48,53-55,57,63,67,84] that used different methodologies to compare the overall survival of patients meeting the MC and patients exceeding the criteria at the time of the explant pathology examination; 3949 patients were also stratified by the graft origin (deceased or living donors).

As outlined in Fig. 2, the hazard ratio of 1.68 [95% confidence interval (CI) = 1.39-2.03] confirmed the significantly increased posttransplant survival expected for patients meeting the MC versus patients beyond the MC. In fact, the MC qualified as the benchmark for LT prognostication in patients with HCC despite the significant heterogeneity in the hazard ratios reported by or derived from the different series because all the studies showed similar trends in favor of patients meeting the MC. When the studies were split according to the type of transplant, the hazard ratio for patients exceeding the MC was 1.76 (95% CI = 1.45-2.15) in the deceased donor category, but it was only 1.28 (with a lower confidence interval limit of 0.86) in the living donor category. This was presumably due to the shortening of the waiting time and the acceleration of transplantation with living donation versus deceased donation (the so-called fast-track effect).[104]

Rapidly progressing HCCs that exceed the MC during the time on the waiting list are not the only factors determining an adverse prognosis when patients do not meet the MC. Obviously, the tumor burden remains the leading factor affecting the prognosis, even though the magnitude of this covariate could not be explored further in this meta-analysis because of the significant heterogeneity of the HCCs exceeding the MC in the collected studies. Recent studies have demonstrated that the risk of adverse outcomes after LT can be strictly correlated to progressive increases in the size and number of HCCs in patients selected for transplantation.[26]

Finally, there are no sound studies of the cost-effectiveness of LT with respect to the MC. The cost of quality-adjusted life years that are gained with LT is generally $35,000 to $125,000[105]; the cost range for living donor LT is even lower.[106]

According to the available data, there is sufficient evidence to establish the MC as the main factor for determining the prognosis after LT. Through the

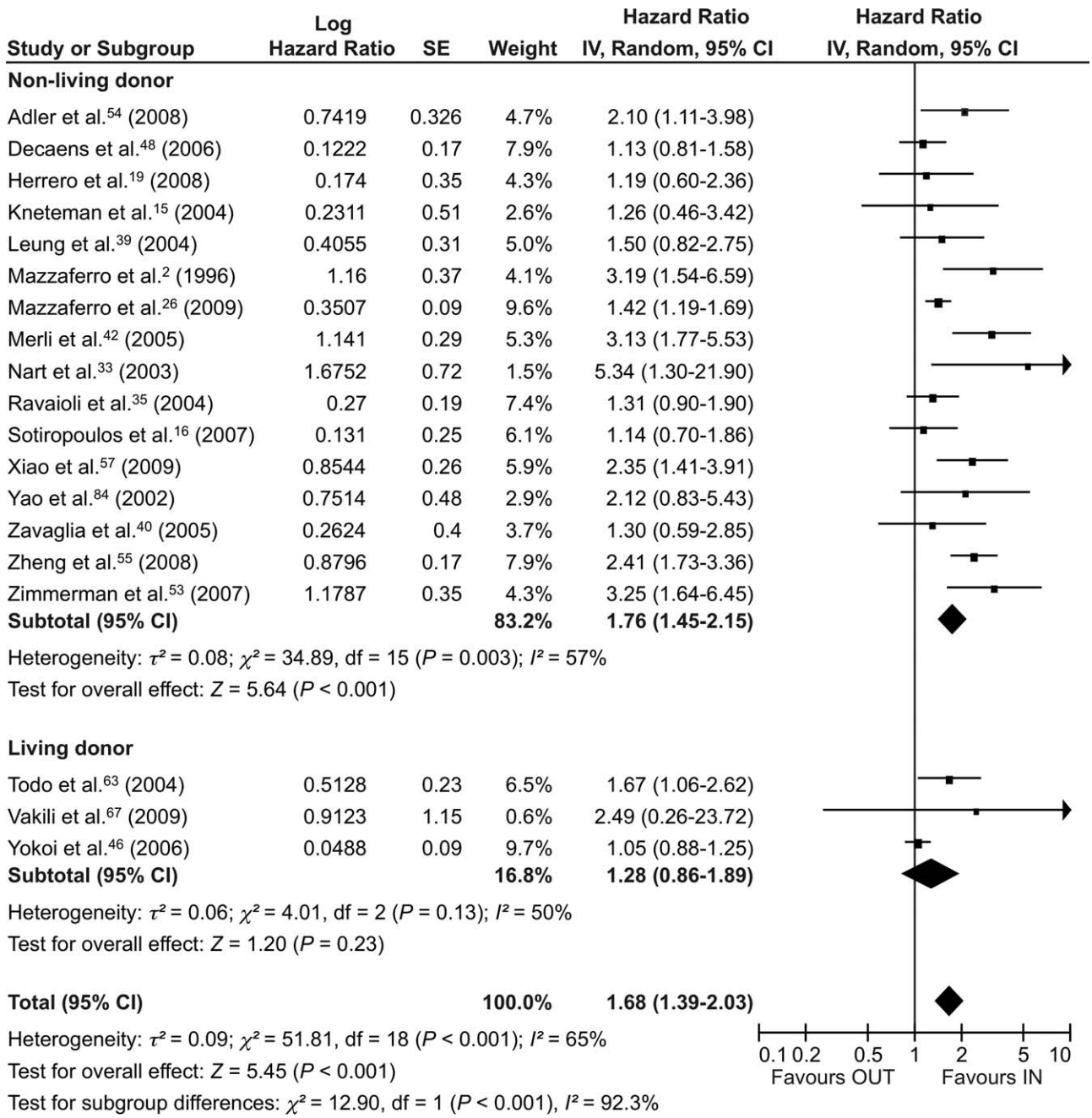


Figure 2. Meta-analysis of the 19 studies comparing the overall survival of patients with HCC meeting the MC and patients with HCC exceeding the MC at the time of the explant pathology examination. The studies are stratified by the graft type (deceased or living donor).

determination of the tumor size and number, the MC currently represent the most reliable composite factor for assessing HCC morphology with respect to patient allocation for transplantation.

An indirect confirmation of the robustness of this conclusion is the current graft allocation policy for patients with cirrhosis and HCC in the large majority of Western countries. According to the modified Model for End-Stage Liver Disease (MELD) score, cadaveric liver grafts are assigned with priority only to patients meeting the MC at the time of pretransplant staging[107] (ie, United Network for Organ Sharing category T2).

In addition, because the potential benefit for patients with HCC meeting the MC is similar to the potential benefit for patients with nonmalignant diagnoses, the use of scarce donor organs for candidates with HCC meeting the MC is highly justified. In this respect, the MC remain the benchmark for any other prognostic criteria proposed for expanding the use of LT in patients with cirrhosis and HCC.

TABLE 3. Literature-Based Findings for Patient, Tumor, and Treatment Characteristics Most Often Associated With Positive and Negative Survival Outcomes for Patients Within the MC at the Time of Transplantation

Patient Characteristics		HCC Characteristics		Therapy-Associated Characteristics	
Positive Outcome	Negative Outcome	Positive Outcome	Negative Outcome	Positive Outcome	Negative Outcome
Female[28,74]	Male[52]	Capsule[27,40,77]	mVI-present[2,13,18–22,26–28,30,32,33,40,43,45,47,51–53,56,57,59–61,63,66,67,70,74,76,77,79,80]	LT (T1 and T2 and up to 5 nodules)[70]	Resection only (recurrence-free survival)[71,76,78–80]
No virus[77]	Hepatitis C virus–positive[21,76]	AFP level <10[39] or <20 ng/mL[63,77]	Macrovascular invasion–present[2,10,13,14,18,19,21,22,27,28,30,32,34,40,45,52,53,57,62,63,66,70,77,80]	TACE before LT[80]	Tumor persistence/recurrence after bridging[23]
	Age >50,[54] >55,[12] or >60 years[52]	Tumor size <3 cm [13,27,45] or <5 cm[43,71]	Satellite-present[14,34,51,72,76]		
	MELD score >30[63]	MC met[2,16,20,21,25,27,40,42,48,51,53,57,58,72,75,77,80]	AFP level >30,[20,35] >100,[39,54] >200,[38] >300,[36,65] >400,[24,40,80] or >1000 ng/mL[12,18,51]		
		Up-to-7 criteria met[21,26]	Tumor size >3 cm,[36,51,70,76] >3.5 cm,[53] >5 cm,[2,10,13,30,37,62,80] >6 cm,[72] or >8 cm[40,50]		
			pT3 and pT4[2,31,53,54,70] or pT4[12,30,33]		
			Total tumor volume >28 cm^3 [35] or >115 cm^3 [24]		
			Total tumor diameter >8 cm[12,42]		
			Bilobar nodules[66]		
			Multiple nodules[52,71,76]		
			Nodule number >3[2,13,64] or >5[30]		
			Grades 2-4[30,43] or grades 3 and 4[12–14,16,20,26,37,40,45,52,57,59,61,63,65,67,76,77,80]		
			Size + number >4[78]		

Does the Application of the MC Lead to Patients With Less Aggressive HCCs Being Considered for LT?

A relevant factor leading to positive post-LT outcomes for patients meeting the MC is the ability of the criteria to select patients for LT whose HCCs have favorable biological characteristics (according to size and number parameters).

With respect to patients exceeding the MC, posttransplant pathology assessments of livers from patients meeting the MC have revealed reduced rates of adverse histological parameters and surrogates of tumor aggressiveness, such as mVI, poorly differentiated tumors, and microsatellites.

Nine level 1b studies[2,13,15,17-21,23] 2 level 2a studies,[25,26] and 13 level 2b studies[27,30,33,34,36,39,40,42,47,48,51-53] have confirmed the likelihood of detecting mVI, grade 3 tumors, and microsatellites as the tumor size and number increase beyond the MC. In patients with HCCs meeting the MC, mVI is detected at a rate of 10% to 15%, poorly differentiated tumors are detected at a rate of 13% to 33%, and microsatellites are detected at a rate of 7% to 28%. For patients not meeting the MC, the rates of mVI and grade 3 and 4 tumors significantly increase (35%-56% and 38%-50%, respectively).[26,48]

Similar rates of histological markers of tumor aggressiveness and poor prognoses have been detected in patients slightly exceeding the MC, such as patients meeting the University of California San Francisco criteria,[52,84] even though a significant proportion of patients meeting the University of California San Francisco criteria are meeting the MC as well.[24,34,47,51]

We identified 10 studies[16,18,26,28,47,48,51,52,63,72] reporting frequency data for mVI and tumor grades in patients meeting or not meeting the MC, and a meta-analysis of the odds ratios was performed accordingly (Fig. 3).

Only the risks of mVI (1883 patients) and poorly differentiated tumors (1808 patients) were investigated in this meta-analysis (Fig. 3). The fact that only 1 study[72] described frequency data for microsatellites related to the MC impeded any meta-analysis aggregation for the microsatellite covariate.

Adherence to the MC was significantly associated with a reduced frequency of tumor grades higher than 2 and a reduced risk of mVI, as shown by odds ratio estimates of 2.54 (95% CI = 1.65-3.91) and 4.88 (95% CI = 3.18-7.48), respectively (Fig. 3). These results confirm the common observation that the size and number limits of the MC identify a subgroup of early-stage HCCs with a low risk of aggressive biological behavior in comparison with expanded indications.

According to the available data, the precise staging of early and very early HCCs for transplant candidacy retains some subjective features, especially because of the current imaging technology and the prognostication power of alpha-fetoprotein (AFP) as a surrogate of biological tumor behavior. Until molecular markers predicting the metastatic potential and/or mVI are validated and are clinically applicable, the identification of HCC patients meeting the MC through size and number determinations can be considered a surrogate tool for the inclusion of patients with less aggressive HCCs on the LT waiting list.

Should Patients Within the MC Be Treated While They Are on the Waiting List for LT?

There is evidence that patients meeting the MC have a lower risk of dropout from the waiting list due to disease progression or death in comparison with patients without HCC.[108] Data from large cohorts in Japan and the United States have confirmed that most patients with early-stage HCC within the MC do not experience significant progression of their cancer for approximately 1 year after they join the waiting list.[17,25,89,109,110] Nevertheless, the risk of dropout due to cancer progression in patients meeting the MC at the time of listing still exists and is as high as 30% if no treatment is pursued; however, bridging therapies during the waiting period (either ablation or locoregional approaches) are able to reduce the dropout rate into the range of 0% to 21%.[111,112] In general, the dropout risk increases as the waiting time progresses; in the case of HCC patients who are listed for more than 3 months, the dropout rate is greater than that observed for patients with nonmalignant diseases.[112]

Although there is no proven posttransplant advantage in treating patients within the MC who are listed for transplantation, the available evidence (average NOS score = 7)[17,22,23,35,80] indicates that listed patients within the MC who are treated while they are on the waiting list with ablation (preferred for single nodules < 3 cm) or transarterial chemoembolization (TACE; preferred for HCCs > 3 cm or with a multinodular pattern) have reduced dropout rates in comparison with historical untreated controls.[23] Although no RCTs have confirmed this, up to 65% of the HCC patients on the Organ Procurement and Transplantation Network waiting list currently receive locoregional treatments. Although precise data for the subset of patients meeting the MC are not available, evidence shows that pretransplant treatments are widely used, regardless of the tumor stage, to prevent dropout from the list and possibly to improve post-LT survival.[111]

In a recent study using a Markov model simulation and restrictive assumptions, sorafenib was shown to be cost-effective in comparison with no therapy for patients within the MC (ie, United Network for Organ Sharing stage T2) who were waiting for transplantation, particularly when the median time to transplantation was <6 months.[113] Molecular-targeted therapies during the LT waiting period for patients with HCC are likely to be tested in the near future.[114-116]

Although the level of evidence is low, the current clinical practice of treating patients with HCCs within the MC who are listed for LT seems justified for the specific endpoint of reducing the dropout rate. Bridging therapies may alter the natural course of the

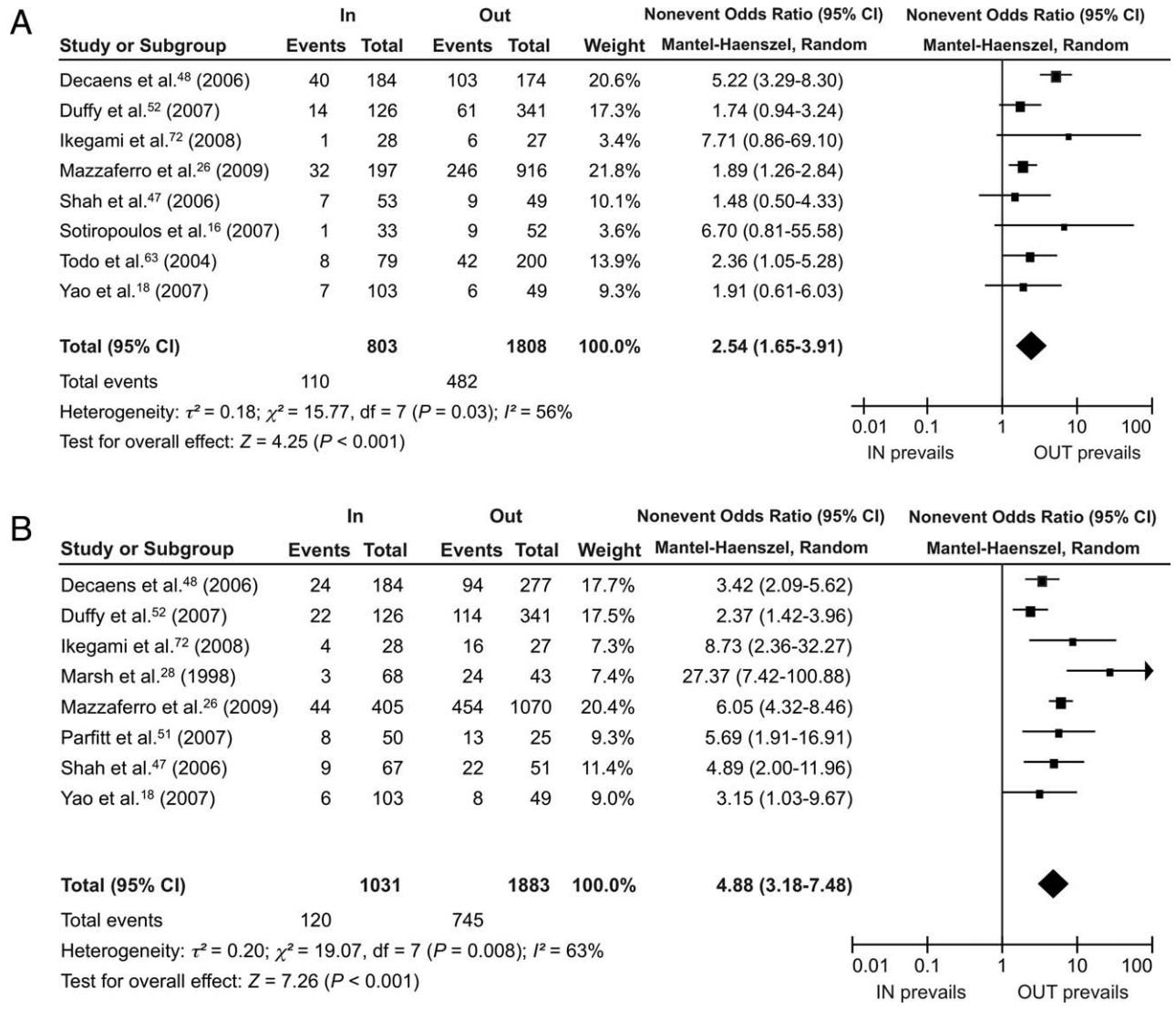


Figure 3. Meta-analysis of the studies comparing (A) the frequency of tumor grades higher than 2 (8 studies) and (B) the presence of mVI [8 studies (6 in common with panel A)] in patients with HCC meeting the MC and patients with HCC exceeding the MC.

disease and may partially explain the discrepancy between observed and expected rates of disease progression.[111]

The paucity of data and the lack of evidence do not allow any firm conclusions about the improvement of posttransplant survival for patients within the MC who receive pretransplant treatments, although some positive effects can be inferred from preliminary experiences with TACE.[117,118]

Additional Findings

Although the suboptimal study quality and the retrospective nature of the analysis are limitations, further information can be collected from this systematic review of the available MC literature:

1. The pretransplant staging of HCCs suitable for LT because they strictly adhere to the MC remains challenging at times. Interestingly, no deterioration in post-LT survival seems to have occurred for patients considered to meet the MC in different imaging technology eras. This may be consistent with the fact that the MC predict good outcomes for patients falling within the assigned limits rather than bad outcomes for patients exceeding them.
2. The risks of understaging the morphological characteristics of tumors and selecting patients with more aggressive HCCs for transplantation increase as much as the MC are exceeded. As a matter of fact, pathology assessments of explants from understaged tumors find significantly more bilobar HCC nodules (37% versus 13%) with mVI (41% versus 15%).[47]
3. In comparison with patients with HCCs exceeding the criteria, patients with HCCs meeting the

MC have median serum AFP levels within lower ranges.[39,63,77] In agreement with the proven role of AFP as a prognostic tool (rather than a diagnostic tool) for HCC, high serum levels of AFP have been correlated with a deterioration in the prognosis of patients with tumors belonging to the MC category, even though a precise cutoff is missing (Table 3). Although the strength of the evidence is impoverished by the suboptimal quality (average NOS score = 6) and the limited number of studies,[12,18,20,24,35,36,38-40,51,54,65,80] AFP in clinical practice represents a quite reliable and noninvasive tool for capturing potentially more aggressive HCCs within the MC. In some centers, values > 400 or >1000 ng/mL are often important determinants for delisting patients otherwise eligible for LT.[24,119,120]

4. Almost no evidence exists for determining whether a state of mind oriented to consider LT as the most effective treatment option for HCC influences any individual strategies against liver cancer. As a matter of fact, an increased number of multistep, individualized treatment options are proposed for difficult HCC cases; each treatment, although it is unvalidated, is proposed according to the supposed adjuvant or neoadjuvant potential for future transplantation. The practice of individualized treatment plans that lack precise investigation schemes for LT in patients with HCC should not be recommended.

SUMMARY AND CONCLUSIONS

This is the first systematic review assessing the value of the MC as an independent prognostic factor affecting the outcomes of LT for the treatment of HCC. A comprehensive search of the literature based on stringent selection criteria produced a list of 90 studies of sufficient quality from 1864 references. In addition, a meta-analysis of 25 sufficiently powered studies allowed the extraction of hazard ratios that significantly proved the prognostic power of the MC and their ability to capture HCCs still retaining favorable biological characteristics.

The chosen methodology has allowed the prognostic implications of MC to emerge with a lower grade of evidence in comparison with pure RCTs. RCTs were prevented for HCC by the striking differences in the posttransplant survival rates observed since the implementation of MC and those of historical controls.

HCCs meeting the MC have been confirmed to be a separate prognostic category associated with good outcomes after LT (a 5-year survival rate of at least 70%). This has prompted the integration of the MC into staging systems, transplant indications, and prioritization policies worldwide.

Although the lack of homogeneity and the presence of noncomparative, retrospective studies hamper any firm conclusions, this review has translated objective MC data into assumptions of significant evidence:

1. The MC are major determinants of the prognosis of patients undergoing LT for HCC. Patients meeting the MC achieve survival benefits similar to those of patients with nonmalignant diagnoses. The results of LT for patients meeting the MC should be the benchmark for any proposal of expanded criteria, which are associated with an increased risk of adverse outcomes in comparison with conventional indications (Fig. 2).
2. The MC identify a subset of patients with a significantly lower risk of tumor grades higher than 2 and mVI (Fig. 3). Until more precise predictors of prognosis using molecular techniques are validated, the MC in combination with the determination of AFP levels remain a reliable and noninvasive instrument for selecting patients with less aggressive HCCs more suitable for LT.
3. Locoregional treatment strategies for patients with HCCs within the MC who are listed for LT (bridging therapies) are justified for the specific endpoint of reducing the dropout of patients from the transplant waiting list. Conversely, the effect of bridging therapies on post-LT survival is not known.
4. Arbitrary treatment plans lacking prospective designs and predetermined endpoints do not facilitate indications beyond the MC and should not be recommended.

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