Predictive Value of Biological Markers for Hepatocellular Carcinoma Patients Treated with Orthotopic Liver Transplantation

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ABSTRACT

Purpose: To help stratify candidates with hepatocellular carcinoma (HCC) for orthotopic liver transplantation (OLT), biomarkers are needed that are capable of predicting recurrence of disease (ROD). We investigated the prognostic role in this setting of immunohistochemical markers reported previously to predict poor prognosis in HCC patients treated with resection.

Experimental Design: Eighty-three patients with HCC who underwent OLT between 1987 and 2001 with a minimum clinical follow up of 12 months were included in this retrospective study. We analyzed immunohistochemical expression of the adhesion molecules E-cadherin and β-catenin (membrane/nuclear localization), MIB-1 proliferative index and the cyclin-dependent kinase inhibitor p27, alongside the main clinical-pathological variables.

Results: At univariate analysis, vascular thrombosis, high MIB-1 index, lower membrane expression of E-cadherin and β-catenin, and nuclear β-catenin localization were associated with ROD. At multivariate analysis, only MIB-1 index, low equal E-cadherin (with respect to non-neoplastic surrounding tissue), and nuclear β-catenin appeared as independent predictors of ROD. The logistic regression analysis model indicated that detection of any one parameter was associated with at least 88% estimated risk of ROD (up to 99% for all three).

Conclusions: We propose these three molecular parameters as an additional tool for rational selection of OLT candidates among HCC patients (stratification according to the risk of ROD might help provide a similar life expectancy for cirrhotic candidates with and without HCC).

INTRODUCTION

Hepatocellular carcinoma (HCC) is a common, deadly malignancy (1), of which the outcome mainly depends on early diagnosis and feasibility of surgical therapies (2). In >80% of patients, the HCC arises in the already unfavorable setting of cirrhosis, most often related to chronic viral hepatitis types B or C (3). The multiple therapies currently available for patients with HCC arising on cirrhotic tissue include locoregional ablative therapies (trans-arterial embolization, radio-frequency thermo-ablation, and alcohol injection), surgical resection, and orthotopic liver transplantation (OLT). OLT is a particularly effective option for single, small (<5 cm) or multiple (up to 3), min (<3 cm) HCC not suitable for surgical resection (4).

Recurrence of disease (ROD) is the most predictive clinical prognostic indicator for all HCC patients. Long-term survival remains poor due to the high incidence of intrahepatic ROD, which occurs (at 5 years) in 60–100% of patients treated with surgical resection (5). By contrast, the prevalence of ROD after OLT is much lower, and the 5-year survival rate is >70% (6, 7). This is because OLT not only removes the tumor but also the residual cirrhotic liver at risk of metachronous lesions and restores normal liver function. Furthermore, because the liver is entirely removed at OLT, any recurrence must derive from extrahepatic dissemination that occurred before or during transplantation, reflecting highly aggressive tumor biology. Given the current organ shortage and the risk of aggressive recurrence, selection of candidates for OLT is a crucial factor and still a matter of debate (8, 9). Efforts are now focused on identifying tumor characters predictive of recurrence that can define a subset of HCC patients that stand to benefit from OLT. Commonly used predictors of recurrence after OLT are histological (tumor size, Edmondson grade, presence of and microvascular invasion; Refs. 9–12) and clinical (Cancer of the Liver Italian Program scoring system) features (13). Data on the capacity of biological markers to reliably predict ROD and survival after OLT are currently lacking (14).

Expression of several biological markers predicts poor prognosis in HCC patients treated with resection or locoregional therapies. A study performed by our group showed that the cyclin-dependent p27 kinase inhibitor is an independent prognostic parameter for HCC (15). Additional studies (16–19) have highlighted the prognostic role of various biomarkers, including cell-cycle regulators, oncogenes and their receptors, apoptosis-related factors, telomerase activity, PTEN tumor suppressor gene, microvessel density, and adhesion molecules including...
β-catenin and E-cadherin (20). In particular, decreased immunohistochemical (IHC) expression of E-cadherin has been related to poor prognosis in patients treated with liver resection for HCC (21–23), whereas conflicting results have been reported on prognostic value of nuclear and non-nuclear β-catenin IHC expression (24–28). In this study we investigated the prognostic role of p27, E-cadherin, β-catenin, and MIB-1 proliferative index in a large series of HCC patients treated with OLT in our institution.

PATIENTS AND METHODS

Patient Population. Eighty-three patients (68 men, 15 women; mean age, 52 ± 8 years; range, 28–64 years) who underwent OLT in our institution between 1987 and 2001 were included in this retrospective study according to the following eligibility criteria: (a) HCC diagnosed either before or after transplantation (as an incidental finding), suitable for treatment with OLT according to the criteria suggested by Mazzaferro [single small (i.e., <5 cm) or up to 3 min (<3 cm) tumors in cirrhosis; Ref. 4]; (b) availability of complete clinical, instrumental, and laboratory data before transplantation and during follow up; (c) availability of sufficient histological archival material for all of the planned immunostaining procedures (see below); (d) minimum post-transplantation follow-up of 12 months (for survivors); and (e) absence of de novo HCC nodules occurring in the transplanted liver. Informed consent was obtained from all of the patients in the study.

Some baseline clinical and pathological characteristics of the study population can be seen in Table 1. Sixty-nine (83%) patients had metastatic disease unrelated to hepatitis C virus, hepatitis B virus, or alcohol. In 27 (33%) patients, HCC was diagnosed as an incidental finding at OLT.

ROD was monitored by means of α-fetoprotein serum levels, ultrasound, and computed tomography. Suspicious lesions were biopsied for histological confirmation of recurrence. Among the 83 patients, 10 (12%) had ROD (median time of diagnosis from OLT, 9 months); all 10 died [median overall survival (OS) from OLT, 20.6 months]. Thirteen of 83 (16%) patients died without ROD from non-neoplastic related diseases (hepatitis recurrence, n = 3; other infections, n = 5; multiple organ failure, n = 3; and neurological complications, n = 2). With a median follow up of 119 months, actuarial OS rates for the 83 patients were 70% at 5 years and 64% at 10 years. None of the patients received postoperative adjuvant antineoplastic therapy.

Tissues. Explanted livers were carefully sampled evaluating all of the macroscopically suspect nodules. Specimens from neoplastic and surrounding non-neoplastic tissue were fixed in 10% buffered formalin. All of the tumors were histologically diagnosed, graded according to Edmonson’s scale (29), and grouped as well-differentiated (grade I-II; n = 40) or poorly differentiated (grade III-IV; n = 43). Tumors were also grouped according to presence of single (n = 42) or multiple (n = 41) lesions, and to presence (n = 61) or absence (n = 22) of microscopic neoplastic vascular invasion. Pathological tumor features are summarized in Table 1.

**IHC Techniques.** Four μm tissue sections were cut, placed on sylane pretreated slides, deparaffinized, and rehydrated through graded alcohols. Antigen retrieval was performed by microwave heating at high power (750 W) in 10 mM sodium citrate buffer (pH 6) for four cycles of 5 min each. Slides were then allowed to cool for 30 min before incubation for 1 h at room temperature with the following monoclonal antibodies, anti-p27 (Transduction Laboratories, Lexington, KY) diluted 1:200, anti-E-cadherin (Dako, Carpinteria, CA) diluted 1:50, anti-β-catenin clone E-5 (Santa Cruz Biotechnology, Santa Cruz, CA) diluted 1:40, and anti-Ki67 (clone MIB-1; Dako) diluted 1:50. Staining was performed with the Envision monoclonal System (Dako). The reaction was developed with 3,3-diaminobenzidine. Slides were counterstained with Mayer’s hematoxylin and mounted. Nonimmune mouse serum was used as negative control.

**IHC Scoring Criteria.** IHC staining was independently evaluated by two pathologists (M. F. and A. D.), who were blinded to clinical data. E-cadherin and β-catenin membranous signal were semiquantitatively assessed comparing the expression in neoplastic and adjacent non-neoplastic liver. HCC were categorized as high expressers or low-equal expressers at the basis of the ratio of nuclei displaying clear-cut positivity with respect to the total number of cells, as described previously (15): tumors were categorized into high p27 expressers (≥50% positive nuclei) and low p27 expressers (<50% positive nuclei). Proliferation index was calculated as the ratio of MIB-1 positive nuclei with respect to the total number of neoplastic cells: tumors were scored as either low proliferating (<10% positive neoplastic cells) or high proliferating (≥10% positive neoplastic cells).
cells). At least 20 high-power fields were randomly chosen, and 2000 cells were counted for each evaluation.

**Data Analysis.** The principle outcome measure was prevalence of ROD. Univariate associations between ROD biologic markers (p27, E-cadherin, β-catenin, and MIB-1) and clinical-pathological variables (sex, age, viral hepatitis, incidental lesions, multiple lesions, grade, and microscopic vascular invasion) were assessed by Pearson’s χ² test and verified by Fisher’s exact test (30). We also considered overall significance (OS; secondary outcome measure, defined as time between the day of OLT to the day of death or the most recent follow-up visit), calculated using the Kaplan-Meier method; the log-rank test being used for univariate analysis with the other variables.

**RESULTS**

**Role of Clinical-Pathological Parameters.** At univariate analysis (χ² test; Table 2), only presence of microscopic vascular invasion significantly correlated with presence of stringently defined ROD (P < 0.05). In particular 61 of 83 (73%) patients showed neoplastic vascular thrombosis including all of the 10 patients with ROD. High histological Edmondson’s grade showed a trend toward correlation (P = 0.052) with presence of ROD, with 8 of 10 (80%) patients with ROD showing HCC grade III or IV. None of the other clinical-pathological features significantly affected ROD. Finally, no significant correlation was found between any of the clinical-pathological features and OS (Table 2).

**Significance of MIB-1 Index and p27 Protein at Univariate Analysis.** Seventy-three of 83 (88%) patients displayed a low MIB-1 proliferative index (<10% of the neoplastic cells; Table 2). Among the 73 patients with low MIB-1 index, 68 (93%) had no ROD. At univariate analysis, high MIB-1 index (Fig. 1A) was associated with presence of ROD (χ² test, P < 0.01), and also correlated with OS (P < 0.005, log rank test; Fig. 2B).

Only 2 of 83 (2%) HCC were high p27 expressers (>50% neoplastic cells), both of which were free of ROD. It should be noted that among the remaining 81 (98%) low p27 expressers (<50% neoplastic cells), 49 (60%) showed expression in <5% nuclei and 32 (40%) in 5–25% nuclei (data not shown). A cutoff of 50% p27 positive nuclei value was used for statistical analysis, as described previously (15). Possibly due to the very low number of p27 high expressers in the series, no relation was observable between high/low p27 expression and ROD or OS.

**Decreased Membrane Expression of E-Cadherin, and β-Catenin and Nuclear β-Catenin Localization Are Associated with ROD After OLT.** All of the normal hepatocytes showed weak to moderate membrane positivity for E-cadherin and β-catenin expression, whereas bile ducts and proliferating ductules showed strong membrane expression of both molecules. Regarding E-cadherin, 34 of 83 (41%) HCC were low-equal expressers at the tumor-normal interface (Fig. 1, C and D). Nine of 10 (90%) of the cases of ROD were low-equal E-cadherin expressers. Regarding membrane β-catenin, 35 of 83 (42%) HCC turned out to be low-equal expressers. Eight of 10 (80%) of the cases of ROD were low-equal membrane β-catenin expressers. Concerning nuclear β-catenin, either focal or diffuse expression was found in only 6 of 83 (7%) HCC (Fig. 1B); staining was never observed in non-neoplastic adjacent parenchyma. Four of 10 (40%) HCC associated with ROD showed nuclear β-catenin expression. At univariate analysis decreased

**Table 2** Univariate analysis of histological features and biological markers with respect to ROD* (Pearson’s χ² test) and OS (log-rank test)

<table>
<thead>
<tr>
<th>Vascular invasion</th>
<th>n</th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>P ROD</th>
<th>Survival status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>61</td>
<td>10 (16)</td>
<td>51 (84)</td>
<td>&lt;0.05</td>
<td>18 (30)</td>
</tr>
<tr>
<td>No</td>
<td>22</td>
<td>0 (0)</td>
<td>22 (100)</td>
<td></td>
<td>5 (23)</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (I–II)</td>
<td>40</td>
<td>2 (5)</td>
<td>38 (95)</td>
<td>0.052</td>
<td>10 (25)</td>
</tr>
<tr>
<td>High (III–IV)</td>
<td>43</td>
<td>8 (19)</td>
<td>35 (81)</td>
<td></td>
<td>13 (30)</td>
</tr>
<tr>
<td>E-cadherin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low–equal expression</td>
<td>34</td>
<td>9 (26)</td>
<td>25 (74)</td>
<td>&lt;0.01</td>
<td>15 (44)</td>
</tr>
<tr>
<td>High expression</td>
<td>49</td>
<td>1 (2)</td>
<td>48 (98)</td>
<td></td>
<td>8 (16)</td>
</tr>
<tr>
<td>Membrane β-catenin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low–equal expression</td>
<td>35</td>
<td>8 (23)</td>
<td>27 (77)</td>
<td>&lt;0.01</td>
<td>12 (34)</td>
</tr>
<tr>
<td>High expression</td>
<td>48</td>
<td>2 (4)</td>
<td>46 (96)</td>
<td></td>
<td>11 (23)</td>
</tr>
<tr>
<td>Nuclear β-catenin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>4 (67)</td>
<td>2 (33)</td>
<td>&lt;0.01</td>
<td>4 (67)</td>
</tr>
<tr>
<td>No</td>
<td>77</td>
<td>6 (8)</td>
<td>71 (92)</td>
<td></td>
<td>19 (25)</td>
</tr>
<tr>
<td>MIB-1 index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>73</td>
<td>5 (7)</td>
<td>68 (93)</td>
<td>&lt;0.01</td>
<td>16 (22)</td>
</tr>
<tr>
<td>High</td>
<td>10</td>
<td>5 (50)</td>
<td>5 (50)</td>
<td></td>
<td>7 (70)</td>
</tr>
<tr>
<td>p27</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low expression</td>
<td>81</td>
<td>10 (12)</td>
<td>71 (88)</td>
<td>N.S.</td>
<td>23 (28)</td>
</tr>
<tr>
<td>High expression</td>
<td>2</td>
<td>0 (0)</td>
<td>2 (100)</td>
<td></td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* ROD, recurrence of disease; OS, overall survival; N.S., not significant.

Additional analyses included in the multivariate analysis. Cox proportional hazard regression model was used for OS, and logistic regression was used for ROD (32, 33). All of the calculations were performed using SPSS 8.0 statistical software package, and the results were considered significant at P < 0.05.
E-cadherin expression was correlated with worse OS (\( P < 0.01 \), log-rank test; Fig. 2A), whereas the presence of nuclear β-catenin showed a trend toward correlation (\( P = 0.052 \)). It is noteworthy that in all of the cases showing nuclear localization of the β-catenin protein, presence of mutations of the β-catenin gene was investigated by single-strand conformation polymorphism PCR, as described previously (34), with mutation analysis of the β-catenin gene at exon 3 being performed after slide microdissection of those areas showing nuclear localization of the protein. A spot mutation was found in 3 of 6 (50%) cases (data not shown).

MIB-1 Index, E-Cadherin, and β-Catenin Are Independent Predictors of ROD After OLT at Multivariate Analysis. To elucidate the independent prognostic factors affecting ROD, multivariate analysis was performed with the parameters that reached significance at univariate analysis. As reported in Table 3, logistic regression indicated that nuclear β-catenin, low-equal E-cadherin expression, and high MIB1 index were independent indicators of early ROD, with odds ratios of 35, 15, and 12, respectively. We used this model to retrospectively calculate the probabilities of developing ROD with each of the possible combinations of high MIB-1 index, low-equal E-cadherin expression, and nuclear β-catenin positivity, according to this model. In particular, when considering the 10 cases that developed ROD, 1 case had nuclear β-catenin only, 3 cases had only low-equal E-cadherin expression, 3 cases had both low-equal E-cadherin and high MIB-1 index, 1 case had low-equal E-cadherin and nuclear β-catenin, and 2 cases showed all three of the parameters. As shown in Table 4, the probability of developing ROD appeared to be 99% in the presence of all three of the conditions and 0% in their absence.

Regarding OS, only high MIB-1 index significantly correlated with poorer outcome (\( P < 0.05 \); Table 3).

DISCUSSION

Our results provide the first evidence that investigation of selected biological parameters can effectively predict ROD in HCC patients treated with OLT. Analysis of data from our series indicates that concurrent detection of high MIB-1 index, low-
equal E-cadherin and nuclear β-catenin positivity in the same patient may be able to predict ROD with a probability of 99%. As can be seen in Table 4, even the presence of just one of these three parameters seems to be associated with at least 88% likelihood of ROD.

The current goal of OLT transplantation teams is to stratify candidates according to their risk of ROD in such a way as to give transplanted cirrhotic patients with and without HCC similar life expectancies (35). In HCC patients, ROD is generally followed by a rapid decline. Thus, stringently defined ROD (as distinct from de novo HCC in the transplanted liver) was the primary prognostic end point of our study. OS is a less relevant end point than ROD, due to the influence of nontumor-related causes of death (including hepatitis, bacterial infections, multiple organ failure, neurological complications, and so forth), which are generally also present in OLT recipients without HCC. When we tested the significance of the same biological parameters on OS, only the high MIB-1 index appeared to be predictive of poor survival.

Taken together, our results are broadly in keeping with the sort of indications that have emerged from reports of MIB-1 index and E-cadherin assessment in the setting of HCC patients treated with surgical resection [Refs. 19, 21–23; although an isolated study (36) paradoxically documented a relation between amount of E-cadherin and invasive potential].

Regarding β-catenin, conflicting reports exist on the prognostic role of its expression and localization in surgically treated HCC (24–28). In our series of OLT-treated patients, decreased expression of membrane β-catenin was associated with ROD only at univariate analysis, whereas its nuclear localization retained independent predictive value at multivariate analysis. These findings may reflect the multifunctional role of the β-catenin protein, either as a regulator of cell-cell adhesion when complexed to E-cadherin or as a nuclear regulator of gene expression along the Wnt/wingless signal transduction pathway. The percentage of cases with nuclear β-catenin localization was lower in our series than in other studies (a discrepancy, which we think might be ascribed to the selected population of OLT patients and perhaps to different geographical distributions of nuclear β-catenin positive HCC). Furthermore, the nuclear positivity was confirmed frequently at gene mutation analysis by single-strand conformation polymorphism-PCR (whereas, regarding the remaining cases, it should be borne in mind that lack of mutation does not exclude other reasons for nuclear localization of β-catenin).

We also examined the significance of the cyclin-dependent kinase inhibitor, p27. In contrast to various studies on surgically treated HCC, we were unable to detect a significant association between decreased p27 expression and poor survival among our OLT recipients. However, this negative finding can probably be ascribed to the very low number (two cases) of high p27 expressers in this series. It is noteworthy that all of the patients treated with surgical resection [Refs. 19, 21–23; although an isolated study (36) paradoxically documented a relation between amount of E-cadherin and invasive potential].

Table 3 Multivariate analysis of the influence of each individual parameter on ROD* (logistic regression) and OS (Cox proportional hazard regression)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>P</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular invasion</td>
<td>N.S.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low–equal membrane β-catenin</td>
<td>N.S.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuclear β-catenin positivity</td>
<td>&lt;0.05</td>
<td>35.406</td>
<td>2.250–557.248</td>
</tr>
<tr>
<td>Low–equal E-cadherin</td>
<td>&lt;0.05</td>
<td>15.038</td>
<td>1.281–176.466</td>
</tr>
<tr>
<td>High MIB-1 index</td>
<td>&lt;0.05</td>
<td>11.677</td>
<td>1.306–104.410</td>
</tr>
<tr>
<td>OS</td>
<td>N.S.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuclear β-catenin positivity</td>
<td>N.S.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low–equal E-cadherin</td>
<td>N.S.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High MIB-1 index</td>
<td>&lt;0.05</td>
<td>3.333</td>
<td>1.006–7.003</td>
</tr>
</tbody>
</table>

* ROD, recurrence of disease; OS, overall survival; CI, confidence interval; N.S., not significant.

Table 4 Risk of developing ROD* according to all the possible combinations of the three significant markers (logistic regression)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Possible combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low–equal E-cadherin</td>
<td>– ++ + – – + – +</td>
</tr>
<tr>
<td>High MIB-1 index</td>
<td>– – – – ++ – + +</td>
</tr>
<tr>
<td>Nuclear β-catenin positivity</td>
<td>– – – + – + + +</td>
</tr>
<tr>
<td>Risk of ROD</td>
<td>0% 88% 92% 89% 88% 93% 90% 99%</td>
</tr>
</tbody>
</table>

* ROD, recurrence of disease.
informative of the predictive value of p27, and more extensive studies are required on this marker in the OLT treatment setting.

Regarding clinical-histological features, some recent studies have suggested that histological grade, presence of vascular invasion, and tumor size might help predict ROD after OLT (7–12). In our series, only vascular invasion was associated with ROD at univariate analysis (with high Edmondson’s tumor grade just showing a trend), but it failed to maintain independent significance at multivariate analysis. The low predictive power of these clinical-pathological parameters in our series might be related to the strict eligibility criteria used for patient selection.

OLT is an excellent therapeutic choice for patients with cirrhosis complicated by HCC, because it provides a simultaneous treatment for both diseases. However, due to the limited availability of organs, prior selection of the candidates most likely to benefit from OLT is very important. In the absence of nontumor-related factors like primary liver dysfunction, rejection, infections, or multiorgan failure, the prognosis of these patients primarily depends on ROD (life expectancy after ROD is very short due to the highly aggressive behavior of the tumor). Prediction of the likelihood of ROD by the above-mentioned biomolecular parameters might help transplantation teams to better select candidates to OLT.

The molecular parameters proposed by us can be assessed on archival histological tissues including biopsies. In particular, MIB-1 index and nuclear β-catenin can be easily assessed on tumor samples with a simple IHC technique. Evaluation of decreased E-cadherin expression requires comparison with adjacent non-neoplastic parenchyma and, thus, provision of larger/multiple biopsy samples. Because most OLT candidates undergo biopsies or locoregional tumor treatments, it would not be a problem to obtain tissue samples for presurgical IHC analysis.

It should be noted that our series inevitably included a relatively low proportion of patients with ROD (because of the much lower risk of ROD after OLT than after resection). This study limitation must be taken into account when considering the estimated levels of risk of ROD (Table 4) associated with the various combinations of the three unfavorable biological parameters, as generated by the logistic regression model (the risk levels ranged from ≥88% for any single parameter to 90% for all three of the parameters). The model appears to be robust because the area under the conventional-ROC curve was >60% and the Hosmer-Lemeshow test was not significant (data not shown). In any case, confirmation is required from larger studies.

In summary, although our findings require confirmation in prospective studies, we propose application of the three molecular parameters described in this study, high MIB-1 index, low-equal E-cadherin, and nuclear β-catenin positivity, as a feasible tool for more rational selection of OLT candidates with HCC. Effective stratification according to the risk of ROD might help attain the selection goal of reaching similar life expectancies for OLT recipients with and without HCC.

ACKNOWLEDGMENTS
We thank Claudio Voci for statistical analysis and Robin M. T. Cooke for scientific editing.

REFERENCES


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