

## ORIGINAL ARTICLE



# Validation of the easy-to-use lenvatinib prognostic index to predict prognosis in advanced hepatocellular carcinoma patients treated with lenvatinib

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## Abstract

**Aim:** The identification of new prognostic factors able to stratify hepatocellular carcinoma patients candidate to first-line therapy is urgent. In the present work we validated the prognostic value of the lenvatinib prognostic index.

**Methods:** Data of Eastern and Western patients treated with lenvatinib as first-line for Barcelona Clinic Liver Cancer stage B or C hepatocellular carcinoma were recollected. The lenvatinib prognostic index was composed by three classes of risk according with our previous study. The “low risk” group includes patients with prognostic nutritional index (PNI)  $>43.3$  and with previous transarterial chemoembolization. The “medium risk” group includes patients with PNI  $>43.3$ , but without previous transarterial chemoembolization and patients with PNI  $<43.3$ , albumin-bilirubin grade 1 and Barcelona Clinic Liver Cancer stage B. The “high risk” group includes patients with PNI  $<43.3$ , albumin-bilirubin grade 2, and patients with PNI  $<43.3$ , albumin-bilirubin grade 1 and Barcelona Clinic Liver Cancer stage C.

**Results:** A total of 717 patients were included. The median overall survival was 20.7 months (95% CI 16.1–51.6) in patients with low risk ( $n = 223$ ), 16.7 months (95% CI 13.3–47.0) in patients with medium risk ( $n = 264$ ), and 10.7 months (95% CI 9.3–12.2) in patients with high risk ( $n = 230$ ; HR 1, 1.29, and 1.92, respectively;  $p < 0.0001$ ). Median progression-free survival was 7.3 months (95% CI 6.3–46.5) in patients with low risk, 6.4 months (95% CI 5.3–8.0) in patients with medium risk, and 4.9 months (95% CI 4.3–5.5) in patients with high risk (HR 1, 1.07, 1.47 respectively;  $p = 0.0009$ ).

**Conclusion:** The lenvatinib prognostic index confirms its prognostic value on an external cohort of hepatocellular carcinoma patients treated with Lenvatinib.

### KEYWORDS

hepatocellular carcinoma, lenvatinib, prognostic factors

## INTRODUCTION

Liver cancer constitutes the third leading cause of cancer death worldwide, with 75%–85% of cases represented by hepatocellular carcinoma (HCC).<sup>1</sup> Despite recent advances, the treatment of HCC still represents a big challenge in the oncologic field, as only approximately 40% of cases are amenable to loco-regional treatment with radical intent, whereas most cases are candidates for systemic treatment.<sup>2</sup> A number of new therapeutic strategies in this setting have been recently investigated, mainly in first-line setting. Sorafenib was the first tyrosine-kinase inhibitor (TKI) to show a survival benefit in unresectable/advanced disease.<sup>3,4</sup> The REFLECT trial showed the non-inferiority of lenvatinib, another TKI, compared with sorafenib as first-line treatment.<sup>5</sup> Recently, data from the phase III IMbrave150 trial led to the establishment of the combination of the anti-

programmed cell death-ligand 1, atezolizumab, and the anti-vascular endothelial growth factor, bevacizumab, as the new standard of care in an advanced HCC setting,<sup>6</sup> and a number of new combinations are currently emerging in this setting with promising results.<sup>7,8</sup> In this context of rapid improvement of the therapeutic armamentarium for advanced HCC patients, the identification of prognostic factors is becoming an urgent need. Several prognostic factors have been identified in patients treated with sorafenib, including neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, albumin-bilirubin (ALBI) score, prognostic nutritional index (PNI), and systemic immune-inflammation index,<sup>9–13</sup> only a few previous studies investigated prognostic factors in patients treated with lenvatinib.<sup>14–21</sup> In a previous work from our research group, the lenvatinib prognostic (LEP) index resulted from a recursive partitioning analysis that was highlighted to be a promising easy-to-use tool to

stratify patients undergoing systemic treatment for advanced HCC. In particular, on the basis of four variables (PNI, a previous trans-arterial chemoembolization [TACE], the ALBI grade and the Barcelona Clinic Liver Cancer [BCLC] stage), the LEP index identified three groups of risk (low-, intermediate-, and high-risk group) that showed statistical difference in terms of OS (29.8, 17.0, and 8.9 months, respectively;  $p < 0.0001$ ).<sup>22</sup> The aim of the present work was to validate the LEP index in an external cohort of advanced HCC patients treated with lenvatinib.

## METHODS

### Study population

The study population was derived from prospectively collected data of patients treated with lenvatinib as first-line for BCLC stage B or C HCC, deemed not eligible for first-line or for re-treatment with surgical or locoregional therapies. The cohort included Eastern and Western populations from Japan, Korea, and Italy between August 2010 and February 2021. Eligible patients and the dose administered were the same as for our previously paper.<sup>18</sup>

The present study was approved by ethics committee at each center, complied with the provisions of the Good Clinical Practice guidelines and the Declaration of Helsinki and local laws, and fulfilled the Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016 on the protection of natural persons with regard to the processing of personal data (number of ethics committee: 113/INT/2021).

### Statistical analysis

Information on clinical features and hematological blood tests carried out at baseline (the day before the start of treatment) was collected.

Fisher's exact test or *t*-test were used to compare the three risk groups of patients depending on the nature of the covariates and their characteristics (binary or categorical, respectively).

Overall survival (OS) was defined as the time interval between the date of the start of treatment with lenvatinib and the date of death or last follow up.

The LEP index was composed of three classes of risk according with our previous study (Figure 1). The first class, renamed "low risk", included patients with PNI  $>43.3$  and with previous TACE. The second class, renamed "medium risk", included patients with PNI  $>43.3$ , but without previous TACE and patients with PNI  $\leq 43.3$ , ALBI grade 1, and BCLC-B. Finally, the third class, renamed "high risk", included patients with PNI  $<43.3$ , ALBI grade 2, and patients with PNI  $<43.3$ , ALBI grade 1, and BCLC-C. The PNI was calculated as albumin level (in g/l) + 0.005  $\times$  lymphocyte count/ $\mu$ l.

We studied the correlation between each risk group according to the LEP index and OS using Kaplan–Meier survival curves, and a two-tailed *p*-value  $<0.05$  was considered statistically significant. A receiver operating characteristic curve was used to evaluate how

well our previously built LEP index performs in terms of a prognostic tool, through the measure of the area under the curve.

The MedCalc package (MedCalc® version 16.8.4) was used for statistical analysis.

## RESULTS

### Sample characteristics

A total of 717 patients with HCC and treated with lenvatinib were included in our analysis. The study sample included 568 men (78.5%) and 149 women (21.5%) with a median age at diagnosis of 71 years (range 33–97 years). Child–Pugh class A was the most highly represented ( $n = 648$ ; 89.9%). A total of 467 patients (64.8%) had BCLC-C disease stage. A total of 404 patients (56.3%) had a PNI  $>43.3$ . A total of 406 patients (56.6%) were previously treated with TACE; 649 patients (90.5%) had ALBI grade 1; 35.6% patients had a  $\alpha$ -fetoprotein level  $>400$  ng/ml. The most common underlying etiology was hepatitis infection from the hepatitis C virus (34.7%), followed by other etiology (21.3%), hepatitis B (26.5), and non-alcoholic steatohepatitis (17.5%; Table 1).

### Survival outcomes according to the LEP index

According to the LEP index, we recognized three risk groups of patients in our sample: the high-risk group included 230 patients, the medium-risk group included 264 patients, and the low-risk group included 223 patients. After excluding the clinical and laboratory parameters related to the LEP index, the clinical characteristics were well balanced between the three groups of risk, except for sex and alkaline phosphatase (Table 2).

At the time of analysis (August 2021), 424 (59.1%) patients were still alive (171 receiving treatment) and 293 (40.9%) had died. The median OS of the entire population was 15.8 months (95% CI 10.0–51.6).

The median OS was 20.7 months (95% CI 16.1–51.6) in patients with low risk ( $n = 230$ ), 16.7 months (95% CI 13.3–47.0) in patients with medium risk ( $n = 223$ ), and 10.7 months (95% CI 9.3–12.2) in patients with high risk ( $n = 264$ ); the low risk hazard ratio (HR) was 1 (reference group), the medium risk HR was 1.29 (95% CI 1.01–1.69), and the high risk HR was 1.92 (95% CI 1.44–2.57;  $p < 0.0001$ ; Figure 2a). Receiver operating characteristic curve analysis showed an area under the curve of 0.69 (95% CI 0.63–0.74;  $p = 0.0001$ ).

Median progression-free survival (PFS) was 7.3 months (95% CI 6.3–46.5) in patients with low risk, 6.4 months (95% CI 5.3–8.0) in patients with medium risk, and 4.9 months (95% CI 4.3–5.5) in patients with high risk; low risk HR 1 (reference group), medium risk HR 1.07 (95% CI 0.87–1.31), high risk HR 1.47 (95% CI 1.17–1.84;  $p = 0.0009$ ; Figure 2b).

The three groups of patients had different percentages of progressive disease at the first computed tomography response assessment (low risk 17.6%, medium risk 12.9%, high risk 27.1%;  $p = 0.003$ ).

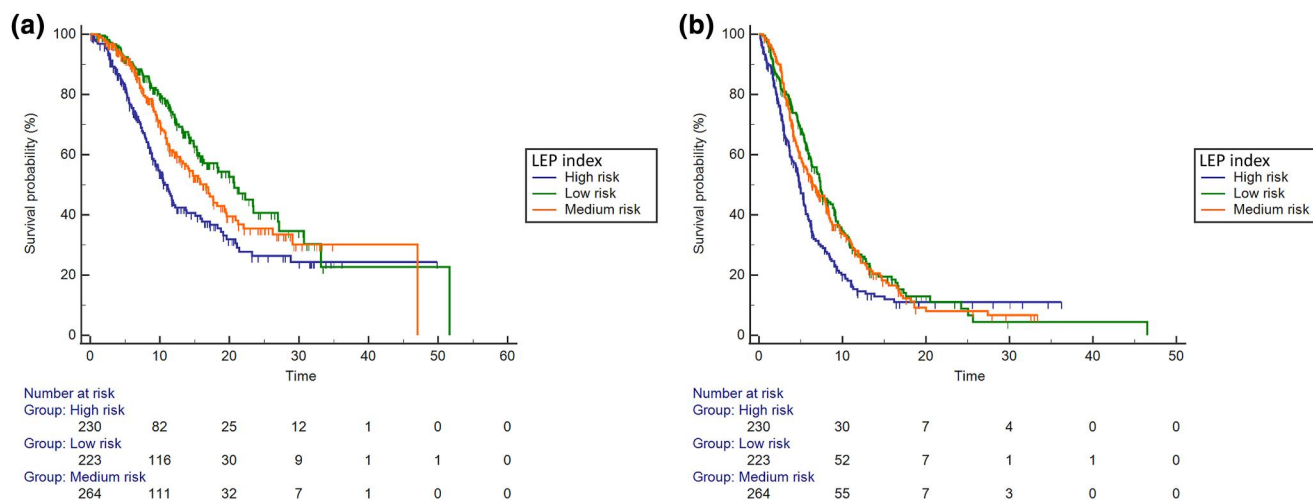


FIGURE 1 Diagram of the lenvatinib prognostic (LEP) index

The objective response rate reported was 39%, 42%, and 29% in low-risk, medium-risk, and high-risk patients, respectively; whereas the disease control rate was 82%, 86%, and 70% for low-risk, medium-risk, and high-risk patients, respectively.

### Survival outcomes in Eastern and Western patients

In the sample study, 106 patients were from Italy and 530 patients were from Asia (Japan and Korea).

In the Italian subgroup of patients, the median OS was 13.6 months (95% CI 11.6–15.7) in patients with low risk ( $n = 40$ ), 12.4 months (95% CI 11.3–13.5) in patients with medium risk ( $n = 39$ ), and 8.8 months (95% CI 6.8–10.9) in patients with high risk ( $n = 26$ ); the low risk HR was 1 (reference group), the medium risk HR was 0.73 (95% CI 0.26–2.09), and the high risk HR was 3.63 (95% CI 0.76–17.25;  $p < 0.0076$ ).

In the eastern subgroup of patients, the median OS was 24.5 months (95% CI 20.3–28.7) in patients with low risk ( $n = 181$ ), 22.8 months (95% CI 19.7–26.0) in patients with medium risk ( $n = 217$ ), and 19.7 months (95% CI 16.5–22.9) in patients with high risk ( $n = 198$ ); the low risk HR was 1 (reference group), the medium risk HR was 1.25 (95% CI 0.94–1.65), and the high risk was HR 1.78 (95% CI 1.32–2.39;  $p < 0.0004$ ).

### Subsequent anticancer medications

Overall, 255 of 717 patients (36%) received subsequent second-line anticancer drug after progression to lenvatinib, with TKIs (including sorafenib, regorafenib, and cabozantinib) being the most commonly administered second-line therapy (138/717, 19%). A total of 71 out of 717 (10%) patients received transarterial chemoembolization as second line, and 18 out of 717 (2.5%) patients received immunotherapy. No statistical differences were found between the high-risk,

medium-risk, and low-risk groups according the LEP index regarding the proportion of patients receiving a second-line treatment ( $p = 0.1580$ ). The median Overall Survival (mOS) for patients receiving or not receiving a second-line treatment was 19.6 versus 14.2 months (95% CI 1.38–1.74;  $p = 0.0061$ ).

### Adverse events

In the low-risk group of patients, 132 out of 223 (59%) patients experienced a grade  $>2$  adverse events; in the medium- and high-risk groups of patients, patients experiencing grade  $>2$  adverse events were 158 out of 264 (59%) and 143 out of 230 (63%), respectively. No statistically significant differences were reported between the three groups of patients in terms of the incidence of grade 3–4 adverse events during treatment with lenvatinib.

### DISCUSSION

In the present study, we validated the LEP index, an easy-to-use score that is able to stratify patients with advanced HCC treated with lenvatinib based on five simple variables: PNI, previous TACE, albumin, bilirubin, and BCLC stage.<sup>22</sup> In the validation cohort, the LEP index was confirmed as a promising tool that is able to stratify patients into three risk groups with different survival outcomes. In particular, a significant difference in terms of OS has been highlighted between the low-, intermediate-, and high-risk groups of patients: 20.7, 16.7, and 10.7 months, respectively. The statistical significance in defining the OS has also been maintained after splitting the population into Eastern and Western patients. In the advanced HCC setting, the prediction of prognosis is particularly complex, as it has to consider both the tumor burden and the liver function. Furthermore, in light to the several new treatments that have recently been proposed for the first-line setting in advanced HCC patients after the

TABLE 1 Baseline characteristics of the cohort

Parameters	N (%)
Median age, years (range)	69 (33–97)
Sex	
Female	190 (21)
Male	731 (79)
ECOG PS	
0	747 (81)
>0	174 (19)
Etiology	
HBV	221 (24)
HCV	320 (35)
NASH	172 (19)
Others	208 (22)
TACE	
Yes	515 (56)
No	406 (44)
ALBI	
1	806 (88)
2	91 (10)
NA	24 (2)
Child–Pugh	
A	820 (89)
B	101 (11)
BCLC stage	
B	348 (38)
C	573 (62)
AFP	
>400 ng/ml	312 (34)
≤400 ng/ml	609 (66)
Albumin	
≤3.5 g/dl	252 (27)
>3.5 g/dl	627 (68)
NA	22 (5)
GPT	
>32 U/L	442 (48)
≤32 U/L	455 (49)
NA	17 (3)
Alkaline phosphatase	
>200 U/L	173 (19)
≤122 U/L	230 (25)
NA	518 (56)

(Continues)

TABLE 1 (Continued)

Parameters	N (%)
NLR	
>3	231 (25)
≤3	429 (47)
NA	261 (28)
PNI	
<43.3	404 (44)
≥43.3	517 (56)

Abbreviations: AFP, alpha fetoprotein; ALBI BCLC stage, Barcelona Clinic Liver Center staging; Child–Pugh, Child–Turcotte–Pugh score; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GPT, glutamic-pyruvic transaminase; Hb, hemoglobin; HBV, hepatitis B virus; HCV, hepatitis C virus; NA, not available; NASH, non-alcoholic steatohepatitis; NLR, neutrophil-lymphocyte ratio; PNI, prognostic nutritional index; TACE, transarterial chemoembolization.

publication of promising data from phase III trials, the definition of clinical manageable tools able to identify patients that could be more likely to benefit from a treatment rather than another treatment is of crucial importance. In fact, the results of the randomized phase III trial IMbrave150 led to the approval of the combination of the anti-PDL1, atezolizumab, plus the anti-angiogenic monoclonal antibody, bevacizumab, as first-line standard of care for these patients.<sup>6</sup> Nevertheless, recent real-world data are currently suggesting that HCC patients with no viral etiology could benefit more from lenvatinib compared with atezolizumab plus bevacizumab.<sup>21</sup> In the near future, further studies will be necessary to define which patients could benefit from a therapeutic strategy rather than another strategy, in an optic of precision medicine, and, probably, lenvatinib will continue to be an important treatment for a group of HCC patients.

Another point deserves attention in the interpretation of the present results: the impact of eventual further lines of treatment after progression to the first line in the retrospective evaluation of survival outcomes of oncologic patients treated with lenvatinib. In the present study, 36% of the sample received a second-line treatment, which included other TKIs, TACE, or immunotherapy. Among the three groups of patients according to the LEP index, no statistical differences were reported regarding the proportion of patients receiving a second-line treatment after progression to lenvatinib, thus reinforcing the stratification capability of the new score.

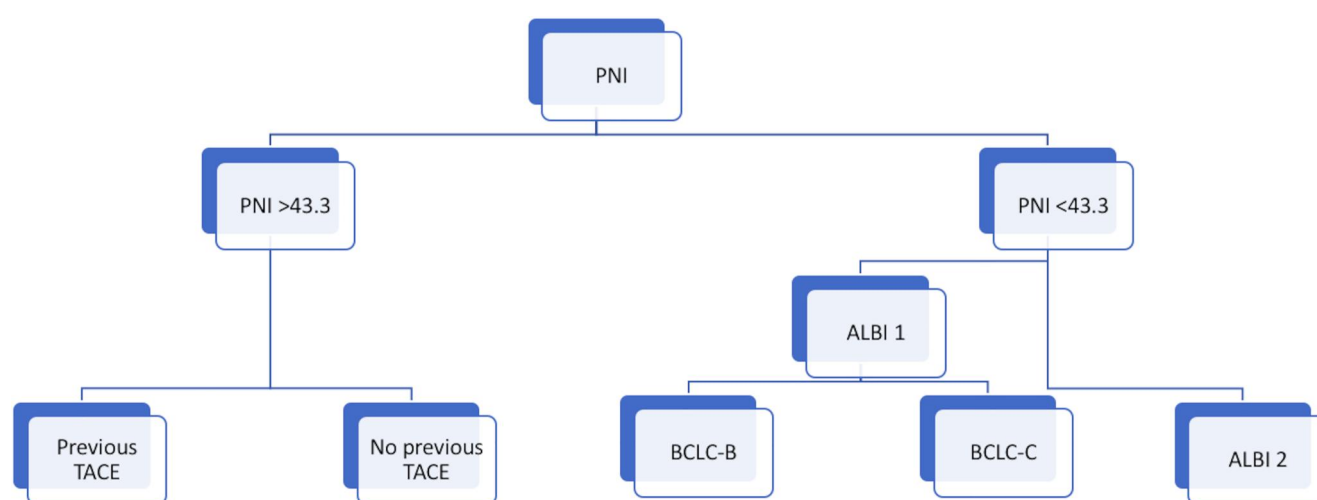
The data we presented are consistent with those reported in our previous work, thus reinforcing the prognostic value of the LEP index previously highlighted.<sup>22</sup> Of note, as in the previous work, the low-risk group of patients performed better in terms of OS if compared with the lenvatinib arm of the REFLECT trial (20.7 vs. 13.6 months), whose OS is located between our intermediate- and high-risk groups' survival date.<sup>5</sup> By analyzing the three groups of risk, several interesting considerations could be explored. The low-risk group constituted patients with PNI >43.3 and who received a previous

TABLE 2 Patients' characteristics in the low-, medium-, and high-risk groups

Parameters	Low risk (N = 223)	Medium risk (N = 264)	Low risk (N = 230)	p
Median age, years (range)	69 (33–94)	68.5 (35–92)	71 (39–97)	
Sex			5	<0.0001
Female	53 (24)	218 (83)	0 (22)	
Male	170 (76)	46 (17)	180 (78)	
ECOG PS				<0.0001
0	200 (90)	244 (85)	148 (64)	
>0	23 (10)	20 (15)	82 (36)	
Etiology				0.2935
HBV	74 (33)	69 (26)	47 (20.5)	
HCV	85 (38)	86 (33)	78 (34)	
NASH	29 (13)	47 (18)	49 (21.5)	
Others	35 (16)	62 (23)	56 (24)	
TACE				<0.0001
Yes	223 (100)	57 (22)	126 (55)	
No	0 (0)	207 (78)	104 (45)	
ALBI				<0.0001
1	223 (100)	262 (99)	162 (70.5)	
2	0 (0)	0 (0)	68 (29.5)	
NA	0 (0)	2 (1)	0 (0)	
Child–Pugh				<0.0001
A	221 (99)	255 (97)	172 (75)	
B	2 (1)	9 (3)	58 (25)	
BCLC stage				<0.0001
B	91 (41)	132 (50)	27 (12)	
C	132 (59)	132 (50)	203 (88)	
AFP				0.5688
>400 ng/ml	77 (35)	87 (33)	91 (40)	
≤400 ng/ml	146 (65)	177 (67)	139 (60)	
Albumin				<0.0001
≤3.5 g/dl	3 (1)	43 (16)	139 (60.5)	
>3.5 g/dl	220 (99)	221 (84)	91 (39.5)	
NA	0 (0)	0 (0)	0 (0)	
GPT				0.1822
>32 U/L	86 (39)	138 (52)	120 (52)	
≤32 U/L	131 (59)	124 (47.5)	108 (47)	
NA	6 (2)	1 (0.5)	2 (1)	
Alkaline phosphatase				0.0283
>200 U/L	40 (18)	44 (17)	65 (28)	
≤200 U/L	85 (38)	84 (33)	42 (19)	
NA	98 (44)	136 (50)	123 (53)	

TABLE 2 (Continued)

Parameters	Low risk (N = 223)	Medium risk (N = 264)	Low risk (N = 230)	p
NLR				0.0010
>3	54 (24)	65 (25)	105 (46)	
≤3	149 (67)	180 (68)	96 (42)	
NA	20 (9)	19 (7)	29 (12)	
PNI				<0.0001
<43.3	9 (4)	85 (32)	230 (100)	
≥43.3	214 (96)	179 (68)	0 (0)	
Second line				0.1580
Yes	93 (42)	96 (36)	66 (29)	
No	130 (58)	168 (64)	164 (71)	



**FIGURE 2** Kaplan-Meier curves for (a) overall survival and for (b) low-, medium-, and high-risk classes according the lenvatinib prognostic index. ALBI 1, albumin-bilirubin index grade 1; ALBI 2, albumin-bilirubin index grade 2; BCLC, Barcelona Clinic Liver Cancer; PNI, prognostic nutritional index; TACE, transarterial chemoembolization

treatment with TACE. In other words, it could be speculated that patients with an earlier stage and who are shown to be refractory to TACE seem to be the ones that may have the major benefit from treatment with lenvatinib. These results are consistent with several previous works that showed a beneficial effect of lenvatinib as early treatment in patients after TACE failure.<sup>24,25</sup> In a previous work from our research group, lenvatinib was shown to perform better compared with sorafenib in patients previously treated with TACE,<sup>26</sup> which is consistent with the present analysis. The theme of combination therapy (locoregional therapy and systemic treatment), as well as of the correct time of association (sequential or concomitant therapy), constitutes a hot topic in the HCC field, mainly if referring to the BCLC-B patients. Indeed, TACE constitutes the only guideline-recommended global standard treatment for intermediate stage HCC.<sup>27</sup> Nevertheless, a significant percentage of the BCLC-B population does not respond to locoregional therapy, thus making the ideation of new treatment approaches able to overcome the survival outcomes of TACE alone an urgent need.

Starting from promising preclinical evidence,<sup>28,29</sup> several trials focusing on the combination of TACE and TKIs have been conducted with heterogeneous results.<sup>30–36</sup> Interestingly, the results from the phase III multicenter randomized controlled combination LAUNCH trial have recently been presented at ASCO 2022, thus highlighting a survival benefit from TACE plus lenvatinib when compared with lenvatinib alone in a cohort of patients affected by advanced HCC with good liver function (mOS 17.8 vs. 11.5 months).<sup>35</sup> Even though the LAUNCH trial reported data from the concomitant use of TACE and lenvatinib, it reinforces the idea that patients treated with TACE might have better survival outcomes under treatment with lenvatinib. Further randomized controlled trials will clarify the real role of the combination of TACE and lenvatinib (as concomitant or sequential treatments) in selected populations of patients affected by HCC.

The intermediate-risk group of patients from the present analysis is constituted by patients who have not previously received TACE, with an ALBI grade of 1 and a BCLC-B stage, whereas the



high-risk group is constituted by patients with ALBI grade of 2 and BCLC-C stage. By comparing the survival outcomes of these two groups of patients with the survival outcomes reported in our previous cohorts, no significant differences in terms of survival outcomes have emerged.<sup>22</sup> In contrast, a lower OS in the low-risk group was highlighted in the validation analysis compared with those of the previous work.<sup>22</sup> It could be ascribed to the different sample size included in the low-risk group of the two analyses (404 vs. 128 patients, respectively), as well as to the different baseline characteristics. Indeed, if considering the whole sample, the cohort of patients analyzed in the present work included a major percentage of patients with BCLC-C HCC and with  $\alpha$ -fetoprotein >400 compared with the previous analysis, which could have influenced the survival results.

Regarding the objective response rate and disease control rate reported in our analysis for the three groups of patients, we highlighted comparable values in low- and medium-risk patients (39% and 82%; 42% and 86%, respectively), whereas patients included in the high-risk group experienced a decreased objective response rate and disease control rate (29% and 70%). From our previous work, the result from the interaction test suggested a possible value of the LEP index in predicting the response to lenvatinib. Nevertheless, the interaction test was conducted on a small size sample of patients. Furthermore, we know that the prognosis of patients affected by HCC is influenced by both tumor burden and treatment response, but also by the residual liver function. Notably, the LEP index includes several parameters that are related to liver function, thus explaining its prognostic role, which do not completely correspond to a clear predictive role.

As already mentioned, nowadays several first-line systemic therapies could be considered for patients with advanced HCC, including sorafenib, lenvatinib, and atezolizumab plus bevacizumab. In our previous work, the application of the LEP index to a cohort of 311 patients treated with sorafenib did not show the same prognostic significance, and the interaction test suggested a possible predictive role of low-risk class in patients treated with lenvatinib. If validated by further prospective investigations, the identification of this predictive role will assume a particular interest, in a setting where several therapeutic options are currently available.<sup>22</sup>

Several significant advantages could be reported regarding the LEP index. First, it was built by using five variables (albumin, bilirubin, lymphocytes, BCLC stage, and previous TACE), which are commonly assessed in clinical practice, and that do not make necessary further examinations and further costs. Second, differing from other prognostic scores designed for the advanced HCC setting, the LEP index includes variables involved with different clinical and biohumoral aspects, including the immune activation (lymphocytes), the hepatic function and metabolic status (albumin, bilirubin), the tumor burden (BCLC stage), and previous locoregional treatments received (previous TACE yes/no). For this reason, the LEP index could be considered a comprehensive prognostic score, which was shown to clearly stratify patients in a validation cohort of advanced HCC patients treated with lenvatinib.

The present study had some limitations. First of all, even though it constitutes the validation on an external cohort of a previously built score, a prospective validation of the score is necessary to establish its prognostic value. Indeed, the retrospective nature of the study could not exclude eventual selection bias, and the different internal protocol in the radiological assessment could have partially influenced the PFS results. In contrast, the present analysis has validated the LEP index on a large external cohort of patients treated with lenvatinib, thus confirming its promising role as an easy-to-use tool able to stratify patients and reinforcing its prognostic value. Further prospective investigations are required to settle the prognostic value of the LEP index, thus translating its use in clinical practice. Furthermore, by testing the index on cohorts of patients treated with different systemic therapy, a potential predictive role could be confirmed, as suggested by our previous analysis.

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## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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