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AFP-DIAM Score to Predict Survival in Patients with Hepatocellular Carcinoma Before TACE: A French Multicenter Study

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Abstract

Background Transarterial chemoembolization (TACE) is recommended as a palliative treatment for patients of the B stage of the Barcelona Clinic Liver Cancer (BCLC) classification.

Aims To identify clinical, biological, and radiological predictors of survival in patients undergoing TACE and develop a pre-therapeutic prognostic score.

Methods 191 adult cirrhotic patients treated for HCC with TACE at the University Hospital (UH) of Clermont-Ferrand (France) from 2007–2017 were retrospectively included. We investigated the impact of baseline liver function, patient characteristics, and tumor burden on overall survival and developed a prognostic score.

Results Patients had a median age of 66 years and 126 patients were Child A. The AFP-DIAM score distinguishes two groups with a significant difference in survival time (median OS 28.3 months in patients with a score = 0 versus 17.7 months in patients with a score > 0). AFP-DIAM was validated on an external cohort, is well calibrated, and has the best discrimination capacity (C-index) as compared to NIACE, HAP, STATE, and SIX TO TWELVE. AFP-DIAM and SIX TO TWELVE are the more easy-to-use scores. When AFP-DIAM and the SIX TO TWELVE scores were tested in the same statistical model, results confirmed a better AFP-DIAM performance.

Conclusions The AFP-DIAM is an easy-to-use score which allows to distinguish two groups with different prognosis before the first TACE session. Its use could provide further support to BCLC system to guide the therapeutic strategy of patients with HCC.

Keywords Hepatocellular carcinoma (HCC) · Chemoembolization · Transarterial chemoembolization (TACE) · Prognostic score

Introduction

Hepatocellular carcinoma (HCC) is the leading cause of primary hepatic tumors and occurs in the vast majority of cases in cirrhotic liver. It is the second leading cause of cancer death in the world and has an incidence of around 9000 new cases per year in France. The current screening scheme allows to diagnose an HCC at an early stage where curative treatment is possible in more than 70% of cases [1]. However, only 20% of patients diagnosed with HCC are included in a surveillance program, resulting in a high percentage of HCC diagnosed at a non-curative stage [2].

In clinical practice, most Western countries use the Barcelona Clinic Liver Cancer (BCLC) classification to choose the adequate treatment [1], TACE is one of the three treatments recommended in patients with intermediate-stage HCC, i.e., stage B of the BCLC classification [preserved hepatocellular function (either CHILD A or B7 without ascites), multinodular HCC without vascular invasion or metastasis and preserved condition (PS 0)]. TACE is offered to patients who cannot benefit from a curative treatment as surgery or transplantation [3, 4].

But this classification presents certain limits: stage BCLC B is very heterogeneous (with very different tumor characteristics and hepatic functions) for only one available therapeutic option, TACE. In addition, certain important prognostic parameters are not taken into account, such as AFP rate or the infiltrative characteristic. Moreover, many patients are treated outside European recommendations, as shown by the international BRIDGE trial where it was reported that almost 50% of patients classified as BCLC C were initially treated by chemoembolization, data confirmed by another international study conducted by Peck-Radosavljevic et al. [5]. These results show that the use of TACE in practice deviates from the recommendations and highlights the need to improve the way patients are treated. Many prognostic scores have been developed to try to identify patients with a poor prognosis for which TACE could be futile and possibly replaced by a systemic therapy: the Hepatoma Arterio-embolization Prognostic (HAP), the Selection for TrAnsarterial chemoembolization TrEatment (STATE) and the NIACE. Only one score was built with prospective data: the six and twelve score [6] but has mainly included patients with hepatitis B. The ART and ABCR scores were developed to try to identify which patients are unlikely to benefit from continuing treatment after one TACE. The retrospective nature of the majority of the studies, the lack of external validation and the differences in the etiological profile of cirrhosis are the main reason why none of the scores is yet part of official recommendations and used in daily practice. Thus, the aims of our work were (i) to identify clinical, biological, and radiological predictors of survival in patients undergoing TACE, (ii) to assess the prognostic value of existing scores, (iii) and to develop a pre-therapy prognostic score, (iv) to validate the score in another French cohort.

Patients and Methods

Inclusion Criteria

All adult cirrhotic patients treated for HCC with TACE at the University Hospital of Clermont-Ferrand (France) from 2008–2017 were retrospectively included. The diagnosis of HCC was made after imaging, according to European recommendations. If the nodule did not have the typical characteristics of a HCC, a biopsy was performed. Then, therapeutic management was discussed at a weekly multidisciplinary consultation meeting. The BCLC stage was defined, and TACE treatment was decided accordingly.

Data Collection

Patients' computer or paper medical charts provided access to consultation letters, biological results and imaging reports. These data were collected retrospectively prior to the first and second TACE. Data to characterize the population and search for prognostic variables were classified into clinical, biological, endoscopic, and radiological data.

TACE Procedures

All the patients were treated by the combination of lipiodol, chemotherapy, and embolization with resorbable gelatin (lipiodol chemoembolization). No embolization alone or intra-arterial chemotherapy without embolization was performed. The chemotherapy drugs used were mainly Epirubicin (50 mg), mixed with Lipiodol (10 mL) as a vector.

Statistical Analysis

Continuous data were expressed according to their statistical distribution, as mean and standard deviation or median with interquartile range. The assumption of normality was assessed by using the Shapiro–Wilk test. Overall Survival (OS) was defined as the interval from date of first cycle to death. OS curves and estimates were determined using the Kaplan–Meier method. The log-rank statistic was used in univariate analysis to test the prognostic value of patient characteristics for the occurrence of the event. Then, a Cox proportional-hazards regression was considered to study the prognostic factors in multivariable analysis by backward and forward stepwise on the factors considered significant in univariate analysis and according to their clinical relevance. The proportional-hazard hypothesis was verified using Schoenfeld's test and plotting residuals. The interactions between possible predictive factors were also tested. Results were expressed as hazard ratios (HR) and 95% confidence interval. The prognostic score was built with the HR values and was then (i) tested in multivariable analysis and (ii) compared with other scores reported in the literature. C-index and AIC (Akaike Information Criterion) values were estimated for each score and were compared. Performance of each score was also estimated calculating sensitivity, specificity, positive predictive value, and negative predictive value. Calibration was assessed using the calibration slope. Statistical analysis was performed using Stata software, version 15 (StataCorp, College Station, US). The tests were two-sided, with a type I error set at 5%.

Results

General Data

Our cohort of 257 patients was treated by TACE between 2008 and 2017. Patients were followed until September 2020. All included patients had cirrhosis. We excluded 66 patients of the analysis: nine women, 23 patients because of missing data, 25 patients for lack of radiological data, and seven patients because of radiological ambivalence, 1 where AFP rate was missing and 1 listed twice. A total of 191 patients were included retrospectively.

Characteristics of the Population

Demographic Characteristics

The study population consisted of men with a median age of 66 years [IQR: 60–71]. Alcohol was the leading cause of cirrhosis in 78% of patients, including mixed etiologies [alcohol associated with NASH (14%) or with hepatitis C (2%)]. Sixty-six percent of patients (126 patients) were classified in stage B of the BCLC classification before the first TACE. The percentage of patients classified as BCLC 0, A, C, and D was 3, 21, 8, and 0.5%, respectively (Table [1](#)).

Patient characteristics

Age (Median [Q1–Q3]) (years) 66 [60–71]

Male patients (%) 191 (100%)

Etiology of liver disease

Alcohol 119 (62%)

NASH 8 (4%)

Hepatitis C 22 (11%)

hepatitis B 7 (4%)

Hemochromatosis 3 (2%)

Other 5 (3%)

Alcohol + NASH 26 (14%)

Alcohol + Hepatitis C 3 (2%)

Ascites

No 177 (93%)

Moderate 13 (6.5%)

Severe/refractory 1 (0.5%)

Hepatic encephalopathy

No 191 (100%)

Yes 0 (0%)

Child Pugh score

A5 116 (61%)

A6 51 (27%)

B7 18 (9%)

B8 5 (3%)

B9 0 (0%)

C 0 (0%)

Unknown 1 (0.5%)

BCLC

0 6 (3%)

A 41 (21%)

B 126 (66%)

C 16 (8%)

D	1 (0.5%)
Unknown	1 (0.5%)
<i>Alcohol withdrawal</i>	
Yes	118 (62%)
< 6 month	25 (13%)
No	42 (22%)
Unknown	6 (3%)
Hospitalization days (Median [Q1–Q3])	5 [5–7]
Post-TACE syndrome	53 (28%)
MELD score (Median [Q1–Q3])	8 [7–10]
Serum albumin (Median [Q1–Q3]) (g/L)	38 [33–40]
Serum bilirubin (Median [Q1–Q3]) (µmol/L)	14 (9–20)
Creatininemia (Median [Q1–Q3]) (µmol/L)	72 [62–87]
Prothrombin's Time (Median [Q1–Q3]) (%)	80 [71–91]
Platelets (Median [Q1–Q3]) (G/L)	127 [85–191]
CRP (Median [Q1–Q3]) (mg/L)	6 [3–10]

Table 1 Main characteristics of the 191 patients treated by chemoembolization

Underlying Liver Assessment

At inclusion, a large majority of patients had compensated cirrhosis, 167 patients (88%) were Child A and 9% Child B. No patient had hepatic encephalopathy and only one patient had refractory ascites. The median bilirubin value before the first TACE was 14 µmol/L [IQR: 9–20], 38 g/L [IQR: 33–40] for albumin, and 80% [IQR: 71–91] for prothrombin time.

Tumor Characteristics

Median AFP was 11.5 ng/mL [IQR: 5.4–68.3] and 28 patients (15%) had AFP value above 500 ng/mL. Seventy-two patients (38%) had 4 or more nodules. The vascularized median diameter of the largest nodule was 41 mm [IQR: 26–59], and one quarter of the patients had a nodule larger than 60 mm (47 patients). The median of the sum of all vascularized diameters of all nodules was 72 mm [IQR: 46–105], and 17% of patients had a sum of > 130 mm. An infiltrating component was found in 9% of lesions, and a significant thrombosis was present in 3% of patients.

Survival Data

Median follow-up was 25 months [IQR: 13–52]. Median overall survival (OS) was 23 months [IQR: 12–43]. Of the 191 patients, 158 (83%) died and 27 (14%) were transplanted.

Univariate Analysis

Statistical analyses were performed only in Child Pugh A and B7 cirrhosis without ascites ($n = 185$). Child > B7 was excluded because of their low number ($n = 5$) and decompensated nature of their cirrhosis. Child B7 without ascites was included, and then the population studied was close to the

guidelines recommendations. Among clinical parameters, only the history of esophageal varicose vein rupture was identified as a significant prognostic factor. Regarding biological data, initial ASAT, bilirubin, and albumin levels were significant predictors of survival.

Among tumor characteristics, AFP rate > 500 ng/mL, tumor size (either the size of the largest diameter or the sum of the diameters), number of nodules, and infiltration character or vascular invasion were significant predictors of survival (Table 2).

Parameters	Hazard ratio	Confidence interval 95%	P-value
<i>Clinical</i>			
Age (years)	0.98	[0.98–1.00]	0.175
Gastrointestinal bleeding	1.76	[1.09–2.82]	0.02
Post-TACE syndrome	1.38	[0.98–1.95]	0.06
<i>Biological</i>			
Bilirubin (μmol/L)	1.02	[1.00–1.05]	0.01
Urea (mg/dL)	1.06	[0.99–1.14]	0.06
ASAT (U/L)	1.00	[1.00–1.01]	0.04
Albumin (g/L)	0.97	[0.94–0.99]	0.01
PT (%)	0.99	[0.98–1.00]	0.11
INR	2.01	[0.69–5.84]	0.20
CRP (mg/L)	1.01	[0.99–1.02]	0.10
> 3 mg/L	1.81	[1.25–2.63]	0.002
<i>Tumor burden</i>			
AFP (ng/mL) > 500 ng/mL	2.06	[1.36–3.12]	0.001
Maximal size (mm)	1.09	[1.04–1.15]	0.001
> 60 mm	1.71	[1.16–2.54]	0.007
Sum of diameters (mm)	1.01	[1.00–1.01]	< 0.001
> 130 mm	1.90	[1.27–2.84]	0.002
Number of nodules	1.18	[1.09–1.29]	< 0.001
≥ 4	1.80	[1.27–2.55]	0.001
Infiltrative tumor	2.70	[1.60–4.60]	< 0.001
Vascular invasion	4.90	[1.96–12.24]	0.001

Table 2 Parameters associated with survival, Univariate analysis ($n = 191$)

Multivariate Analysis

Some values were not used for the multivariate analysis. This is the case of vascular invasion and the infiltrating character of the tumor because these characteristics are difficult to assess outside an expert radiologic center and cannot be used in daily practice. Moreover, the information provided by these characteristics overlaps with the AFP rate and tumor volume, which are easier to define. We chose to keep the parameter “sum of diameters” because it reflects, in our opinion, in a more comprehensive way the tumor volume than the number of nodules. We, therefore, selected 5 significant variables from the univariate analysis: ASAT, Albumin, CRP, AFP rates, and the sum of diameters. In the multivariate analysis, only the combination of AFP rate and sum of diameters were independently predictive of death ($p = 0.002$). These variables were significantly associated with overall survival independently of each other (Table 3).

Parameters	Hazard ratio	Confidence interval 95%	<i>P</i> -value
AFP > 500 ng/mL	1.8	[1.1–2.7]	0.01
Sum of diameters > 130 mm	1.6	[1.1–2.5]	0.03
Combination AFP – Sum of diameters	1.85	[1.26–2.73]	0.002

Table 3 Parameters associated with survival, Multivariate analysis ($n = 191$)

AFP-DIAM Score Construction

With this significant combination in multivariate analysis, we developed a score on the data of our 185 patients, Child Pugh A and B7, treated at the University Hospital of Clermont-Ferrand by two consecutive TACE in order to distinguish different prognostic groups. With the aim to respect the prognostic value of each parameter, we assigned a number of points corresponding to the adjusted hazard ratio in the univariable model (HR 2.06 for AFP > 500 ng/ mL and HR 1.90 for the sum of diameters > 130 mm). This one was almost similar for the two parameters. Thus, the equal weighting was applied to each parameter: 2 points were awarded in case of AFP rate above 500 ng/mL and 2 points in case of sum of diameters over 130 mm. The score was defined as the sum of points. 136 patients had a score of 0 (74%), 39 patients had a score of 2 (21%), and 10 patients had a score of 4 (5%). Then, because of the small number of patients with a score of 4, we separated our population into only two groups with statistically different prognosis: 136 patients had a score of 0 and 49 patients had a score higher than 0. In the good prognosis group (score = 0), the median overall survival was 28.3 months [IQR 14.2–53.0]. In the group with a score > 0, the survival median was 17.7 months [IQR 8.3–24.5] (Fig. 1). Patients with a score > 0 had a 2.2 higher times risk of death [95% CI: 1.6–3.1] compared to patients with a score of 0 ($p < 0.001$).

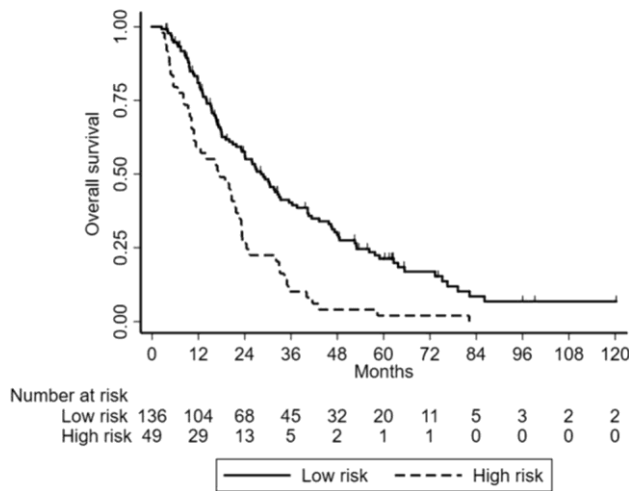


Fig. 1 Kaplan–Meier curve of overall survival for HCC patients treated with TACE according to the AFP-DIAM score ($n = 185$)

External Validation

Characteristics of the Population

For external validation, we used a cohort from the University Hospital of Dijon. The 99 patients were treated by TACE between 2008 and 2012. Patients were followed until August 2013. As in our cohort, we excluded women ($n = 10$). The main characteristics were comparable between the two populations.

Discriminative Ability of the AFP-DIAM in the Dijon Cohort

The score was calculated in the 89 patients of Dijon. When we grouped into two groups (score = 0 and score > 0), the median overall survival was statistically significantly different, 29 months (score = 0) versus 10 months (score > 0) ($p < 0.001$) (Fig. 2).

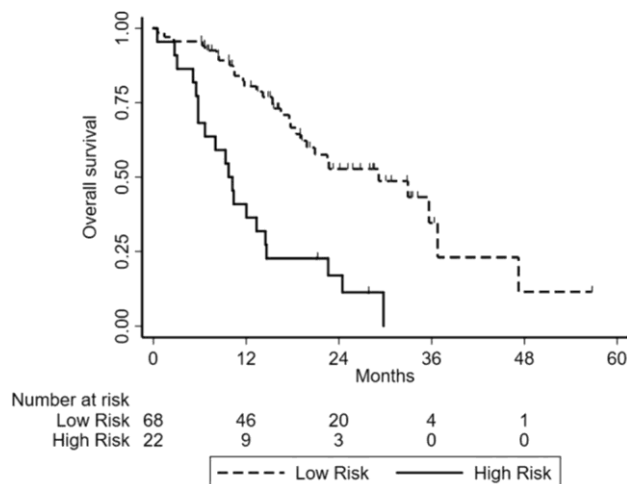


Fig. 2 Kaplan–Meier curve of overall survival for HCC patients treated with TACE according to the AFP-DIAM score, Dijon's cohort ($n = 89$)

Discriminative Prognostic Value of the Existing Scores in Our Cohort

We also assessed the prognostic value of existing scores in our cohort. The prognostic scores (HAP, NIACE, STATE, SIX TO TWELVE SCORE), distinguish groups with a median overall survival statistically significantly different. In our study, the six and twelve score has allowed to differentiate only two groups of patients and not three groups as in the original study: patients with a score lower or equal to 12 versus higher than 12. The median survival was respectively 9.3 (4.6–21.4) months in the > 12 group, 27.1 months (14.2–53) in the ≤ 6 group, and 23.3 (12.4–46.4) months in 6–12 group. The difference was not significantly different between the last two groups.

Calibration of the AFP-DIAM Score

We have studied the calibration of AFP-DIAM score graphically. As shown in Fig. 3, the calibration was very good.

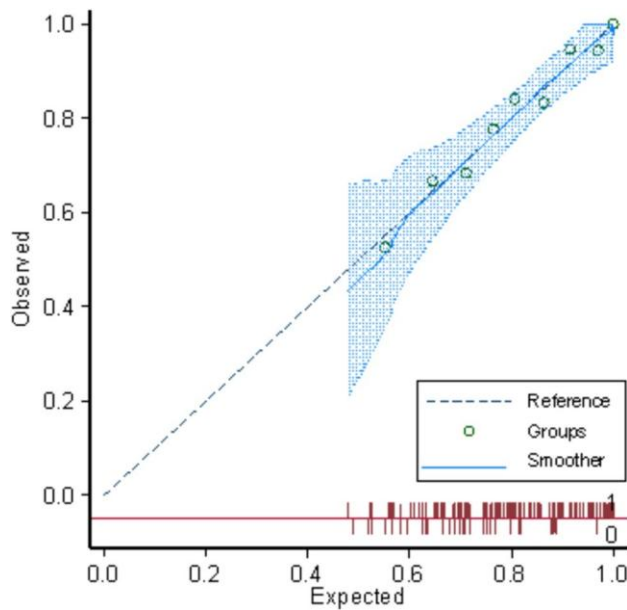


Fig. 3 Graphical representation of the calibration of the AFP-DIAM score

Performance and Discriminative Value of the AFP-DIAM Score and the Four Other Models

The prognostic value of our score was compared to existing prognostic models (HAP, NIACE, STATE, and SIX TO TWELVE). All have been studied in patients undergoing TACE. We studied the performance of the five scores at three years (to reduce competing risks) by calculating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (Table 4).

	AFP-DIAM	HAP	NIACE	SIX TO TWELVE	STATE
Sensitivity (%)	32	30	19	11	26
Specificity (%)	100	88	97	100	91
Positive predictive value (%)	100	92	97	100	93
Negative predictive value (%)	24	21	21	20	22

Table 4 Comparison of the performance (Se, SP, PPV, NPV) of the five prognostic scores at three years

We can notice that the sensitivity of AFP-DIAM was quite low but is higher than the other scores. The PPV was excellent. Using the C-index, the AFP-DIAM score showed the best discrimination capacity (exæquo with the HAP score). Using Akaike information criterion (AIC), AFP-DIAM score showed the second best predictive performances, after STATE score (Table 5).

Score	C-index	AIC
AFP-DIAM	0.58	1310
HAP	0.58	1311
NIACE	0.54	1323
SIX TO TWELVE	0.56	1312
STATE	0.55	1203

Table 5 Assessing discriminative value of the five prognostic scores with the C-index and AIC (Akaike information criteria)

On multivariate analysis (we include at the same two scores), the prognostic value of AFP-DIAM score was superior to that of NIACE, STATE and SIX TO TWELVE models. HAP has an independent prognostic value when includes at the same time HAP and AFP-DIAM. In all the analyses, the AFP-DIAM keeps its independent prognostic value, for example, when we include AFP-DIAM and SIX TO TWELVE scores in the same model. The AFP-DIAM keeps its independent prognostic value with an HR of 2.11 (CI: 1.41–3.14), $p < 0.0001$. The SIX TO TWELVE score has no independent prognostic value: 1.21 (0.67–2.20), $p = 0.53$.

Discussion

The AFP-DIAM score distinguishes two groups of patients with very distinct prognoses among the patients who will benefit from a first TACE session: on one side, a favorable prognosis group with a median survival of 28.3 months and, on the other side, a median survival of 17.7 months for the poor prognosis group. The AFP-DIAM was also validated in an external cohort from another French center. The score has a good calibration and discriminative value. C-index (0.58) of AFP-DIAM score was

superior to that of HAP, NIACE, SIX AND TWELVE, and STATE models, which have also been validated in patients undergoing TACE.

This score is simple to calculate and could be used in daily practice as an aid to therapeutic choice. The prognostic value of the two parameters of our score is consistent with the results of pre-existing studies. An AFP value > 500 ng/mL was significantly associated with a 2.06 higher risk of death. Its prognostic value has also been demonstrated many times in patients treated with TACE [7–9], as well as its association with tumor aggressiveness (satellite lesions and microvascular invasion) [10, 11]. For this reason, AFP concentration is included in many existing prognostic scores such as HAP [12], NIACE [13], and ABCR [14]. We chose a threshold of 500 ng/mL because this value is consistent with the literature (HAP with a threshold of 400 ng/mL, NIACE score with a threshold of 200 ng/mL), and it allowed an acceptable distribution of patients between the two groups (15% versus 85%). We have also chosen to integrate the sum of the diameters into the score. This measurement is easy to achieve even outside expert centers. The threshold of 130 mm was associated with survival. Moreover, it allowed an acceptable distribution of patients (17% versus 83%). It has been shown that tumor size is associated with the risk of vascular invasion and distant metastasis [15] and that the tumor response after TACE will depend on the initial tumor size [16]. The nodular size is already used in several existing prognostic scores such as HAP [12] and STATE [17], but these scores use the size of the largest nodule. To our knowledge, no score has yet used the sum of the diameters of all nodules. We think that this parameter is more representative of the entire tumor volume. In the same way, for several years, volumetric approaches have been developed to try to assess the tumor in its entirety. Lin et al. even determined a 3D volume RECIST (vRECIST) [18, 19]. In Europe, according to EASL recommendations [20], TACE is recommended as a palliative treatment in patients with intermediate-stage HCC (stage B of the BCLC classification). It can also be used for curative purposes while waiting for a liver transplant or for “down-staging” to allow a tumor to get into the transplant criteria. In our study, we, therefore, included Child A and B7 patients without ascites, to be as close as possible to daily practice. There were few patients with ascites-free Child B ($n = 18$). We did not include patients with Child B7 with ascites or more, unlike Kadalayil et al. [12] for the HAP score, Hucke et al. [17] for the STATE score, and Johnson et al.

[21] for the Albi score. These patients have decompensated cirrhosis before treatment and have a much greater risk of degradation of their hepatocellular function after TACE, with less liver reserve, which can have a significant impact on their prognosis and the future therapeutic treatments. As suggested by Tandon and Garcia-Tsao [22], “the compensated patients factors related to the tumor would be more important, whereas in the decompensated patient, both liver- and tumor-related factors would be important to consider.”

Infiltrative HCC is a radiographically distinct and advanced form of hepatocellular carcinoma with a poor prognosis, with a more aggressive character and does not appear to be a good candidate for chemoembolization [23]. Infiltrative HCC is more often associated with vascular or biliary invasion [24]. Its characterization lacks objective criteria and its assessment is difficult, even in expert centers, therefore, not usable in daily practice. Moreover, the information provided by these characteristics overlaps with the AFP rate and tumor volume, which are easier to obtain. Thus, we did not include this parameter in our score. This parameter was included in the NIACE score [14] and the HKLC [25].

The prognostic value of the AFP-DIAM score was confirmed in an independent and external cohort. The median survival rates were comparable to our cohort between the two groups. All the radiological data in our cohort were collected blindly by a radiologist, unlike most other prognostic studies that are often based on patient’s chart (radiologist’s report). Although the BCLC classification has been established as the reference in Western countries, this classification has certain limits, notably for the intermediate stage, BCLC B, with a very heterogeneous tumor profile for a single palliative

therapeutic option available, TACE. In front of a panel of patients, tumor and liver functions are very heterogeneous, which according to the BCLC classification have an indication for treatment by TACE. Moreover, many patients (particularly BCLC C) are treated by TACE outside European recommendations [26, 27] which highlight the need for a new consensus on its indication. For several years, prognostic scores have been developed as a complementary aid. They are based on the hepatocellular function, tumor characteristics, and general condition of the patient. Their aim was to select the right candidates for TACE in order to improve the therapeutic strategy. None is currently recommended by the scientific societies but the AFP-DIAM score in addition to the BCLC system may be useful to guide the therapeutic strategy by assigning to patients in the poor prognosis group (median overall survival of 17.7 months), a systemic treatment such as the association Atezolizumab-Bevacizumab (median overall survival of 19.2 months [26]) or selective internal radiation therapy [27], rather than TACE.

The performance of our score was compared to the four other scores. We can notice that the sensitivity is low but was higher than the other scores. Its positive predictive value is excellent and is as good as or better than the other scores.

We have also shown that AFP-DIAM is well calibrated and has the best discrimination value (C-index) of all the scores. When we include the AFP-DIAM score with another score (one of the four scores) in a multivariate analysis, we have shown that our score keeps its independent prognostic value.

There are limitations to our study. Its retrospective character may be exposed to a risk of missing data. Indeed, we had to exclude 48 patients because of incomplete data at the beginning of our work. We also excluded women because of their limited number. Finally, the prognostic value of the AFP-DIAM score should be validated in a larger prospective multicenter study.

Conclusion

We developed a reliable and easy-to-use prognostic score for patients with HCC undergoing TACE, distinguishing two groups with different prognoses. A score > 0 identifies patients with the worst prognosis who are probably unsuitable for TACE session (median overall survival of

17.7 months versus 28.3 months for the more favorable prognosis group). This score had a better prognostic value and discrimination capacity than other prognostic staging systems for HCC, and has been validated on an independent dataset. It is also well calibrated. Its use could provide further support to BCLC system to guide the therapeutic strategy of patients with HCC.

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