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Risk stratification of patients with hepatocellular carcinoma undergoing trans arterial chemoembolization using an alpha-fetoprotein model

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Abstract

Background: Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide. There are multiple factors that could affect the malignancy and progression of HCC including tumor number, size, and macrovascular invasion. The alpha-fetoprotein (AFP) model was validated as a predictor for HCC recurrence post-liver transplantation, especially in France. However, the AFP model has not been studied on patients with HCC undergoing locoregional treatment. This study aimed to assess the prognostic value of the AFP model in patients with HCC undergoing trans arterial chemoembolization (TACE). This cohort study was conducted at Ain Shams University Hospitals, Cairo, Egypt. We included all newly diagnosed patients with HCC who were fit for TACE from January 2012 to January 2017. The AFP model was calculated for each patient before TACE. Subsequently, we classified them into low- and high-risk groups for TACE. The patients were followed up by AFP level and triphasic spiral CT performed 1 month after TACE to evaluate the response then at 4 months and 7 months post TACE to evaluate the local and distant recurrence.

Results: One hundred and thirty-two patients were included in the study. Complete response (CR) was achieved nonsignificantly at a higher percentage in the low-risk group in comparison with the high-risk group. One- and three-year recurrence-free survivals (RFS) were longer in the low-risk group in comparison with the high-risk group (50% and 24.1% vs. 29.1% and 16.2%, respectively). One- and three-year overall survival (OS) rates were 97% and 37.3% in the low-risk group vs. 98.1% and 11.6% in the high-risk group, respectively, without statistical significance. On classifying patients with AFP levels < 100 IU/mL into low- and high-risk patients, CR was achieved in a significantly higher percentage in the low-risk group in comparison with the high-risk group ($P < 0.05$). Recurrence occurred nonsignificantly in a less percentage in low than high-risk group. The median OS was significantly higher in the low-risk group in comparison with that in the high-risk group (18 vs. 16 months respectively) ($P < 0.01$).

Conclusion: The AFP model may have a prognostic value for patients with HCC undergoing TACE especially in patients with an AFP level < 100 IU/mL.

Keywords: Hepatocellular carcinoma, Egypt, Alpha-fetoprotein model, Trans arterial chemoembolization, Response, Recurrence

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Background

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second most frequent cause of cancer-related deaths worldwide [1]. In Egypt, HCC accounts for 23.81% of all malignancies and constitutes 70.48% of all liver tumors [2]. Hepatitis C virus (HCV) infection is the most common cause of HCC in Egypt with more than 92.5% of patients infected with genotype 4 [3–6]. There are different treatment modalities for HCC including curative measures like liver transplant, surgery, radiofrequency ablation, and other palliative measures like trans arterial chemoembolization (TACE) [7]. There are multiple factors that could affect the malignancy and progression of HCC including tumor number, size, and macrovascular invasion, which are evaluated by radiological imaging before treatment [8]. Prognosis is also affected by the degree of hepatic dysfunction, patient comorbidities, and tumor biology [9]. Recently, the French study group for liver transplantation reported on a new predictive model for HCC recurrence, called the alpha-fetoprotein (AFP) model. They added AFP level to tumor size and number of nodules at listing which increased the accuracy for predicting recurrence after liver transplantation, which was shown to be superior to the Milan criteria in predicting recurrence in patients with HCC. It was validated in a cohort of French patients followed prospectively under the control of the French organization for organ sharing [10]. Therefore, it was officially adopted in January 2013 in France for selecting HCC candidates for liver transplantation [10]. However, the AFP model has not been studied on patients with HCC undergoing locoregional treatment with respect to response to treatment and HCC recurrence.

Methods

The aim of the current study was to assess the prognostic value of the AFP model in patients with HCC undergoing TACE.

This retrospective cohort study was performed at the Tropical Medicine department at Ain Shams University Hospitals, Cairo, Egypt. The study was approved by the Research and Ethical Committee of Faculty of Medicine, Ain Shams University, Cairo, Egypt in accordance with local research governance requirements. We included all newly diagnosed patients with HCC who were fit for TACE according to the Barcelona Clinic Liver Cancer (BCLC) staging 2012 from January 2012 to January 2017. The enrolled patients had been followed up till death or till the end of the study in January 2020. All patients with extrahepatic metastasis, gross vascular invasion, Child class C patients, BCLC stage C or D, patients lost to

follow-up, or patients with any other medical comorbidities as (heart failure, renal failure, respiratory failure, etc.) were excluded from the study. All included patients were subjected to:

Pretreatment assessment

1. Full personal history taking, thorough clinical examination and laboratory investigations including complete blood count, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, serum bilirubin, serum albumin, prothrombin time, AFP level, HCV antibody (Ab), hepatitis B surface antigen, and serum creatinine.
2. Radiological investigations: abdominal ultrasound: for liver size, echogenicity, presence of hepatic focal lesion and their size, site, and number with assessment of portal vein status. All cases underwent triphasic abdominal computed tomography (CT) scan to confirm the diagnosis of the HCC by the presence of arterial enhancement of the focal lesion followed by washout in the porto-venous and delayed phases. Magnetic resonance imaging abdomen with diffusion was ordered if CT criteria were inconclusive or atypical.

Subsequently, the AFP model was calculated for each patient in the study before TACE according to the following (simplified, user-friendly version of the AFP model) [8]:

1. Largest diameter of the hepatic focal lesion (≤ 3 cm, 3–6 cm, and > 6 cm were points 0, 1, and 4, respectively).
2. Number of nodules (1–3 and ≥ 4 were points 0 and 2, respectively).
3. AFP levels (IU/mL) ≤ 100 , 100–1000, and > 1000 were points 0, 2, and 3, respectively.

Then the patients were classified into two groups according to the AFP model: low-risk group for TACE (total points ≤ 2) and high-risk group for TACE (total points of > 2).

The patients were considered eligible for TACE when they had HCC with BCLC stage B. TACE was performed in our HCC unit in Ain Shams hospitals, Cairo, Egypt, which is considered a highly specialized unit established to provide appropriate care for Egyptian patients with HCC. All patients were followed up by AFP, laboratory investigations, and triphasic spiral CT performed 1 month after TACE to evaluate the response and then every 3 months to evaluate local and distant recurrence. The response criteria were defined using the modified

Response Evaluation Criteria in Solid Tumors (mRECIST) [11] to assess hepatic or extrahepatic tumor. In mRECIST, complete response (CR) was defined by complete disappearance of any intra tumoral arterial enhancement in all target lesions. Partial response (PR) was defined as at least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions. Stationary disease (SD) was defined as any case that does not qualify for either PR or progressive disease. Progressive disease (PD) was defined as an increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started. HCC recurrence was calculated in patients who achieved CR in the first follow-up.

At the end of the study, the calculated model was used to predict the response to treatment, HCC recurrence, and overall survival (OS) in low- and high-risk groups. Disease-free survival (DFS) was calculated from the time of the procedure to the time of disease recurrence. OS was calculated from the time of intervention to death or last follow-up visit.

Data management and statistical analysis

IBM SPSS statistics (V. 21.0, IBM Corp., USA, 2012) was used for data analysis. We used mean, standard deviation (\pm SD), and range for parametric numerical data and median and interquartile range (IQR) for nonparametric numerical data. We used Student's *t* test, Mann–Whitney *U* test (*U* test), chi-squared test, Fisher's exact test, Kaplan–Meier survival analysis, and log-rank test in analytical statistics. The confidence interval (CI) was set to 95%, and the margin of error accepted was set to 5%. Therefore, the *P* value was considered significant as follows: *P* > 0.05, nonsignificant (NS); *P* < 0.05, significant (S); and *P* < 0.01, highly significant (HS).

Results

One hundred and thirty-two patients were included in the study with mean age 57.28 ± 7.46 years, male predominance (77.3%) and HCV Ab–positive predominance (89.4%). The mean level of total bilirubin was 1.14 ± 0.45 mg/dL, and the mean level of INR was 1.22 ± 0.17 . The median AFP level was 39.5 IU/mL (IQR: 13.2–301.5). Seventy-nine patients (59.8%) had AFP levels less than 100 IU/mL, 30 patients (22.7%) had AFP levels between 100 and 1000 IU/mL, and 23 patients (17.4%) had AFP levels more than 1000 IU/mL. Most of the patients were Child A (119 patients (90.2%)), while 13 patients (9.8%) were Child B. As for BCLC staging, 64 patients (48.5%) were BCLC A, and 62 patients (47%) were BCLC B. Their

mean model for end-stage liver disease score was 9.83 ± 2.6 . Most of the patients were within Milan criteria (71 patients (53.8%)). The median number of nodules was 1 (range 1–6), while the mean size of the largest nodule was 4.32 ± 1.99 cm (range 1–12 cm).

One hundred and seven patients (81.1%) achieved CR after TACE according to mRECIST, 21 patients (15.9%) achieved PR, 2 patients (1.5%) achieved SD, and 2 patients (1.5%) had PD. Recurrence occurred in 80 patients (74.8%) after intervention. The median OS was 18 months (SE 0.993 with 95% CI 16.053 (lower) and 19.947 (upper)). One and three-year survival was 77% and 9.4%, respectively. The median RFS was 6 months (SE 0.428 with 95% CI 5.161 (lower) and 6.839 (upper)). The one and three-year RFS rates were 38% and 7.7%, respectively. In classifying our patients into Childs A and B, it was found that CR was achieved in a higher number of patients of Child class A (97 patients (81.5%)) than in Child class B (10 patients (76.9%)). PR occurred in a higher percentage of patients of Child class B (3 patients (23.1%)) than Child class A (18 patients (15.1%)). Two patients of Child class A had SD, but none of Child class B had SD or PD, all without reaching statistical significance (*P* > 0.05). Recurrence occurred in a higher percentage of patients of Child class B (9 patients (90%)) than Child class A (71 patients (73.2%)). The median OS in Child class A was 17 months (range 3–42 months), and 15 months (range 8–32 months) in Child class B. None of these results reached statistically significant differences between the two groups (*P* > 0.05).

Majority of our patients were classified as high-risk by the AFP model (75 patients (56.8%)) (Table 1).

Complete response was achieved in a higher percentage of patients in the low-risk group (52 patients (91.2%)) than in the high-risk group (55 patients (73.3%)). Conversely, PR occurred in a higher number of patients in the high-risk group (16 patients (21.3%)) than in the low-risk group (5 patients (8.8%)). Two patients in the high-risk group had SD, and another

Table 1 Classification of patients according to the AFP model before TACE

AFP model		<i>n</i> = 132
Score	Median	2
	Range	0–7
Classification	Low-risk	57 (43.2%)
	Median	0
	Range	0–1
	High-risk	75 (56.8%)
	Median	3
	Range	2–7

Table 2 The AFP model as a predictor of response, recurrence, and survival in patients undergoing TACE

TACE		Low-risk n = 57	High-risk n = 75	P value	Sig.
Response	Complete response	52 (91.2%)	55 (73.3%)	0.057	NS
	Partial response	5 (8.8%)	16 (21.3%)		
	Stationary disease	0 (0.0%)	2 (2.7%)		
	Progressive disease	0 (0.0%)	2 (2.7%)		
Recurrence	No recurrence	15 (28.8%)	12 (21.8%)	0.403	NS
	Recurrence	37 (71.2%)	43 (78.2%)		
	Range	10–42	3–32		
Survival	Negative	37 (64.9%)	59 (78.7%)	0.079	NS
	Positive	20 (35.1%)	16 (21.3%)		

NS Nonsignificant

two patients of the same group had PD. Recurrence occurred in a higher number of patients of the high-risk group (43 patients (78.2%)) than in the low-risk group (37 patients (71.2%)). None of these reached statistically significant differences between the two groups (Table 2).

The median OS in the low-risk group was higher than that in the high-risk group (32 months vs. 29 months, respectively). The 1-year OS rate was nearly similar in both groups (97% in the low-risk group and 98.1% in the high-risk group), while the 3-year OS rate was higher in the low-risk group than in the high-risk group (37.3% vs. 11.6%) but without reaching statistical significance (Table 3) (Fig. 1).

Low-risk patients had a higher median RFS (12 months) than high-risk patients (6 months). The 1- and 3-year RFS rates were higher in the low-risk group than in the high-risk group (50% and 4.8% vs 27% and 0.0%, respectively) (Table 4) (Fig. 2).

Patients with AFP levels less than 100 IU/mL achieved CR in 84.8% of patients. CR occurred in 73.5% in patients who had AFP levels between 100 and 1000 IU/mL, and 78.9% in patients with AFP levels above 1000 IU/mL. There was more recurrence in patients with AFP levels less than 100 IU/mL (49 patients (73.1%)) than in patients with AFP levels between 100 and 1000 IU/mL (21 patients (84%)). However, surprisingly, in AFP levels >1000 IU/mL, recurrence occurred in 10 patients representing 66.7% (Table 5).

In cases with AFP levels < 100, CR was achieved in a significantly higher number of patients in the low-risk group (52 patients (91.2%)) than in the high-risk group (16 patients (69.6%)) in contrast to PR which was achieved in a higher percentage of the high-risk group (4 patients (17.4%)) than the low-risk group (5 patients (8.8%)) with only 2 patients of the high-risk group achieving SD and one patient achieving PD. Recurrence occurred in a lesser percentage of patients in the low-risk group (37 patients (71.2%)) than in the high-risk group (43 patients (81.2%)) but without reaching a statistically significant difference between the two groups. The median OS was significantly higher in the low-risk group (18 months) than in the high-risk group (16 months). The median RFS was higher in the low-risk group (13 months) than in the high-risk group (6 months) but without reaching a statistically significant difference between the two groups (Table 6).

On dividing Child A cases into 2 subgroups according to alpha-fetoprotein model, the median recurrence-free survival was significantly higher in the low-risk group ($P = 0.028$). Also, the median overall survival was highly significant among the low-risk group ($P = 0.000$) (Table 7).

On dividing Child B cases into 2 subgroups according to alpha-fetoprotein model, there was no statistical significance between the 2 groups regarding response and recurrence. Although the median recurrence-free survival and median overall survival were higher in the low-risk group, they did not reach statistical significance (Table 8).

On dividing BCLC A cases into 2 subgroups according to alpha-fetoprotein model, there was no statistical significance between the 2 groups regarding response and recurrence. Although the median recurrence-free survival and median overall survival were higher in the low-risk group, they did not reach statistical significance (Table 9).

On dividing BCLC B cases into 2 subgroups according to alpha-fetoprotein model, there was no statistical significance between the 2 groups regarding response and recurrence. Although the median recurrence-free survival was higher in the low-risk group, it did not reach statistical significance. Only the median overall survival

Table 3 Overall survival (OS) in low- and high-risk patients according to the AFP model

Risk level	OS (months)		95% CI		P value	Sig.	Survival (%) at	
	Median	SE	Lower	Upper			1 year	3 years
Low-risk	32	4.441	23.295	40.705	> 0.05	NS	97.00%	37.30%
High-risk	29	6.169	16.908	41.092			98.1%	11.6%

OS, Overall survival, NS nonsignificant, CI Confidence interval

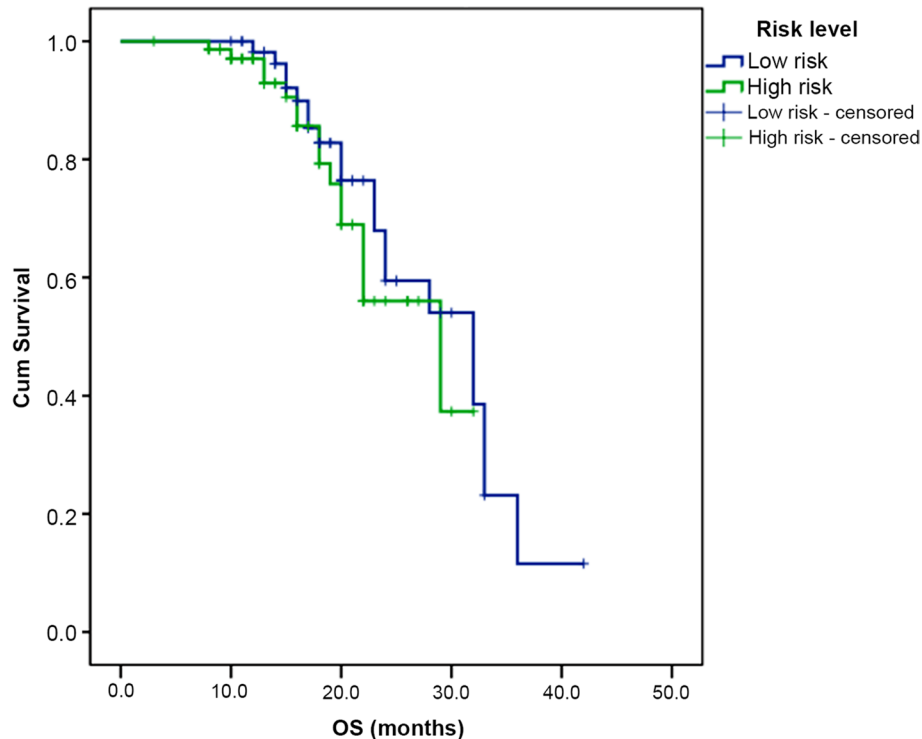


Fig. 1 Kaplan–Meier curve comparing overall survival in low- and high-risk patients

was significantly higher in the low-risk group ($P = 0.003$) (Table 10).

Discussion

HCC is the fifth most common cancer and the second most frequent cause of cancer-related deaths globally. It represents about 90% of primary liver cancers and is considered a major world health problem [1]. In Egypt, HCC is a significant public health problem and is responsible for 33.63% and 13.54% of all cancers in males and females, respectively [12].

The AFP model was proposed as a prognostic tool which was designed in a French training cohort of HCC candidates for liver transplantation and tested further in an external, prospectively followed, validation set. It has been shown to be more accurate than the Milan criteria for selecting HCC candidates for liver transplantation in

the French population, and as a result, it was adopted as an official selection tool by the French organization for organ sharing in 2013 [10, 13]. However, to our knowledge, the AFP model has not been tested as a prognostic tool for patients with HCC undergoing TACE (with respect to response to treatment, HCC recurrence, and survival). Therefore, the present study is the first to assess the prognostic value of the AFP model in patients with HCC after TACE.

The mean age in our patients was around 58 years with male predominance (77.3%). *El-Zayadi et al.* [14] reported that there was a slight shift in age distribution among Egyptian patients with HCC from > 60 years to the age group 40–60 years. The relatively younger age in the Egyptian patients can be explained by the high prevalence of HCV among Egyptians and the occurrence of the infection at a young age. This is in agreement with other Egyptian studies which showed a shift in age in Egyptian

Table 4 Recurrence-free survival (RFS) in low- and high-risk patients

Risk level	RFS (months)		95% CI		P value	Sig.	Survival (%) at	
	Median	SE	Lower	Upper			1 year	3 years
Low-risk	12	1.989	8.101	15.899	> 0.05	NS	50.0%	4.8%
High-risk	6	0.355	5.305	6.695			27.0%	0.0%

RFS Recurrence-free survival, NS Nonsignificant, CI Confidence interval

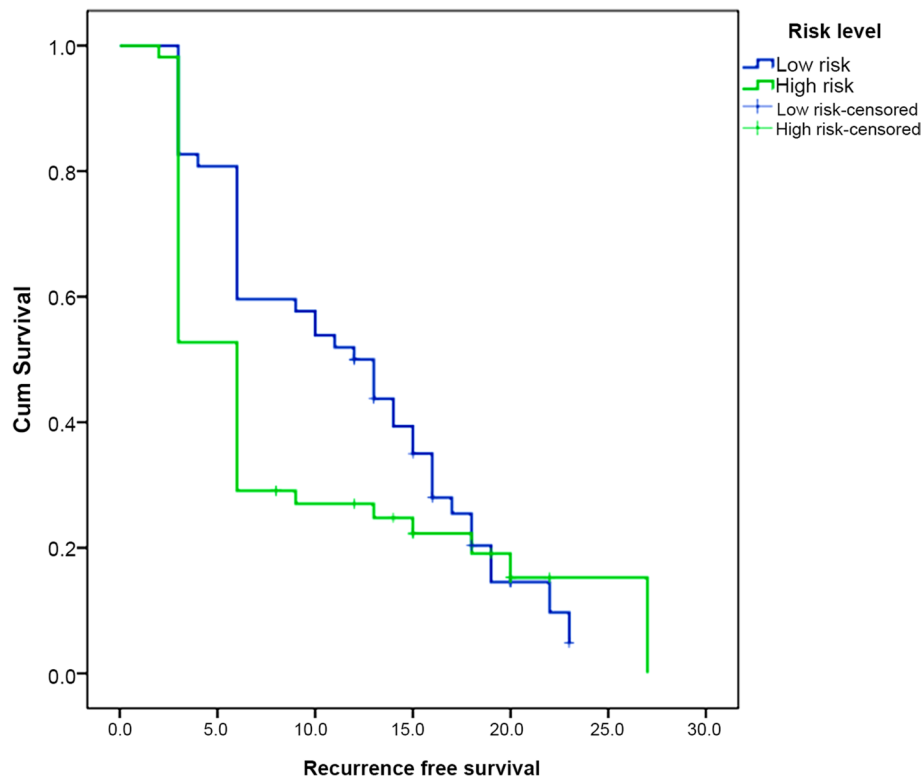


Fig. 2 Kaplan–Meier curve comparing recurrence-free survival in low- and high-risk patients

patients with HCC [15, 16]. Most of the patients included were HCV Ab–positive (89.4%). It is known that Egypt has a high prevalence of HCV infection with 92.5% of patients infected with genotype 4 [3–6].

According to the latest European Association for the Study of the Liver (EASL) guidelines with respect to the locoregional treatment of HCC, thermal ablation with radiofrequency is the standard of care for patients with BCLC 0 and A tumors not suitable for surgery. Thermal ablation in single tumors 2–3 cm in size is an alternative to surgical resection based on technical factors, location

of the tumor, and hepatic and extrahepatic conditions. TACE is recommended for patients with BCLC stage B and should be carried out in a selective manner [1]. An Egyptian study concluded that unresectable HCC with segmental vascular invasion could be treated with TACE with favorable outcome [17]. A proportion of patients in each stage do not fulfill all the criteria for the treatment allocation. In these cases, the patient should be offered the next most suitable option within the same stage or the next prognostic stage. This is already known by the concept of treatment stage migration [18]. Most of our

Table 5 Response and recurrence in different AFP levels in the studied patients

		TACE n = 132		
		AFP level < 100 IU/mL n = 79	AFP level 100–1000 IU/mL n = 34	AFP level > 1000 IU/mL n = 19
Response	Complete response	67 (84.8%)	25 (73.5%)	15 (78.9%)
	Partial response	9 (11.4%)	9 (26.5%)	3 (15.8%)
	Stationary disease	2 (2.5%)	0 (0.0%)	0 (0.0%)
	Progressive disease	1 (1.3%)	0 (0.0%)	1 (5.3%)
Recurrence	No recurrence	18 (26.9%)	4 (16.0%)	5 (33.3%)
	Recurrence	49 (73.1%)	21 (84.0%)	10 (66.7%)

Table 6 Response, recurrence, OS, RFS in patients with AFP levels < 100 after classification into the low- and high-risk groups by the AFP model

		Low-risk n = 57	High-risk n = 22	P value	Sig.
Response	Complete response	52 (91.2%)	16 (69.6%)	< 0.05	S
	Partial response	5 (8.8%)	4 (17.4%)		
	Stationary disease	0 (0.0%)	2 (8.7%)		
	Progressive disease	0 (0.0%)	0 (0.0%)		
RFS (months)	Median	13	6	> 0.05	NS
	Range	3–36	3–30		
Recurrence	No recurrence	15 (28.8%)	3 (18.8%)	> 0.05	NS
	Recurrence	37 (71.2%)	13 (81.2%)		
OS (months)	Median	18	16	< 0.01	HS
	Range	10–42	3–30		

RFS Recurrence-free survival, OS, Overall survival, NS Nonsignificant, S Significant, HS Highly significant

patients were Child A (90.2%). About 48.5% of the patients were BCLC A, and 47% were BCLC B. This is explained by the facts that some lesions were large (> 4 cm) and others were located near the main bile duct, the intestinal loop, or a blood vessel, so radio frequency ablation could not be done, and TACE was the second-best option for them. This is compatible with stage migration in the treatment of HCC as documented in EASL practice guidelines 2018 concerning the management of HCC [1].

In the current study, 81.1% achieved CR, and recurrence occurred in about 74.8% of patients. Median OS was 18 months, while the 1 and 3-year OS were 77%

and 9.4%, respectively. The one and three-year RFS rates were 39% and 20%, respectively. Lencioni et al., [18] published a systematic review on conventional TACE, which included 101 articles, with 10,108 patients. The objective response rate defined as the sum of CR and PR was 52.5%, which is much less than that of the current study where the objective response rate was 97% (CR = 81.1%, PR = 15.9%). The OS was 70.3% at 1 year which is less than that of the current study (77%). The 3-year OS was also higher (40.4%) than that in our study (9.4%). The median OS was 19.4 months vs. 18 months in the current study. In a similar study [19], the tumor response in 129 patients with HCC was evaluated 3 months after the first TACE. In the conventional TACE group, the disease was controlled in 79.8% of patients, which is less than that of the current study where it was controlled in 98.5% of patients. CR was 23.1%, which is much less than that in the current study (81.1%). PR was 26.3% which was more than the current study (15.9%). SD was also higher than that in the current study (30.4% vs. 1.5%). PD occurred in 20.2% of the cases in contrast with the only 1.5% of the current study. Kloeckner et al. [20] reported that the median survival was 409 days (13.6 months) in the conventional TACE group, which is less than that of the current study (18 months).

In the current study, it was observed that the more the liver functions were impaired, the more the increase in the recurrence rate. Recurrence occurred in 73.2% of Child class A and in 90% of Child class B. The median OS was 17 months in Child class A and 15 months in Child class B. The 1- and 3-year OS were 77.9% and 10.3%, respectively, in Child class A, and 69.2% and 0%, respectively, in Child class B. This is compatible with an Egyptian study performed by Zeeneldin et al. [21] who studied 221 patients with HCC who underwent TACE in the

Table 7 Classifying Child A cases into low- and high-risk groups for TACE according to the AFP model

		Child A		Test value	P value	Sig.
		Low-risk No. = 52	High-risk No. = 67			
Response	Complete response	48 (92.3%)	49 (73.1%)	7.799*	0.050	NS
	Partial response	4 (7.7%)	14 (20.9%)			
	Stationary disease	0 (0.0%)	2 (3.0%)			
	Progressive disease	0 (0.0%)	2 (3.0%)			
Recurrence	No recurrence	15 (31.2%)	11 (22.4%)	0.957*	0.328	NS
	Recurrence	33 (68.8%)	38 (77.6%)			
Recurrence-free survival	Median (IQR)	13 (6–18)	6 (3–16)	– 2.198≠	0.028	S
	Range	3–36	3–30			
OS (months)	Median (IQR)	18.5 (15.5–24.5)	16 (10–20)	– 3.713≠	0.000	HS
	Range	10–42	3–30			

Table 8 Classifying Child B cases into low- and high-risk groups for TACE according to the AFP model

		Child B		Test value	P value	Sig.
		Low-risk	High-risk			
		No. = 5	No. = 8			
Response	Complete response	4 (80.0%)	6 (75.0%)	0.043*	0.835	NS
	Partial response	1 (20.0%)	2 (25.0%)			
	Stationary disease	0 (0.0%)	0 (0.0%)			
	Progressive disease	0 (0.0%)	0 (0.0%)			
Recurrence	No recurrence	0 (0.0%)	1 (16.7%)	0.741*	0.389	NS
	Recurrence	4 (100.0%)	5 (83.3%)			
Recurrence-free survival	Median (IQR)	12 (6–17)	4.5 (3–15)	– 0.829 \neq	0.407	NS
	Range	3–24	3–29			
OS (months)	Median (IQR)	18 (15–22)	12.5 (9–25.5)	– 0.882 \neq	0.378	NS
	Range	13–24	8–32			

period between January 2007 and December 2010 and reported that the median OS in Child A was 21 months, which is more than that of the current study (17 months), and 11 months in Child B, which is less than that of the current study (15 months). The results of the current study are close to that of *Kloeckner et al.* [20] who found that the median OS of the subgroup of Child A patients, was 602 days for conventional TACE, which is equal to 20 months. Moreover, the results of the current study are very close to that of *Greten et al.* [22], which had the same median OS in Child A patients as that of the current study (17 months), while patients with Child B had a lower median survival rate of 6 months vs. 14.5 months in the current study.

Prognosis after locoregional treatment is affected by many factors including degree of hepatic dysfunction, patient comorbidities, tumor biology, level of AFP, number of nodules, and size of largest nodule [8, 9]. Several studies used the AFP level alone as a prognostic factor for

HCC post intervention like *Riaz et al.*'s [23] which studied 125 patients with baseline AFP higher than 200 ng/mL and found that a 50% decrease in AFP levels resulted in a better time to progression and OS in comparison with patients whose AFP levels failed to respond to treatment with TACE or trans arterial radioembolization; another study also evaluated the percentage decline in tumor marker levels after treatment (from pretreatment levels) in patients who underwent TACE [24]. The reductions in both AFP and PIVKA-II levels in patients exhibiting a CR or PR were significantly greater than that in those with SD or PD according to the mRECIST criteria. They also found significant differences in median OS times between tumor marker responders and nonresponders.

Several studies used the tumor size [25–27] and number of tumor nodules [28, 29] as predictors of response, recurrence, and survival for HCC after locoregional treatment. Others used the AFP level in combination

Table 9 Classifying BCLC A cases into low- and high-risk groups for TACE according to the AFP model

		BCLC A		Test value	P value	Sig.
		Low-risk	High-risk			
		No. = 38	No. = 26			
Response	Complete response	35 (92.1%)	20 (76.9%)	2.944*	0.086	NS
	Partial response	3 (7.9%)	6 (23.1%)			
	Stationary disease	0 (0.0%)	0 (0.0%)			
	Progressive disease	0 (0.0%)	0 (0.0%)			
Recurrence	No recurrence	9 (25.7%)	7 (35.0%)	0.532*	0.466	NS
	Recurrence	26 (74.3%)	13 (65.0%)			
Recurrence-free survival	Median (IQR)	12.5 (6–17)	8.5 (3–16)	– 1.177 \neq	0.239	NS
	Range	3–36	3–27			
OS (months)	Median (IQR)	18 (15–22)	16 (12–22)	– 1.452 \neq	0.146	NS
	Range	10–42	8–32			

Table 10 Classifying BCLC B cases into low- and high-risk groups for TACE according to the AFP model

		BCLC B		Test value	P value	Sig.
		Low-risk	High-risk			
		No. = 14	No. = 53			
Response	Complete response	12 (85.7%)	34 (70.8%)	1.730*	0.630	NS
	Partial response	2 (14.3%)	10 (20.8%)			
	Stationary disease	0 (0.0%)	2 (4.2%)			
	Progressive disease	0 (0.0%)	2 (4.2%)			
Recurrence	No recurrence	4 (33.3%)	5 (14.7%)	1.956*	0.162	NS
	Recurrence	8 (66.7%)	29 (85.3%)			
Recurrence-free survival	Median (IQR)	12.5 (3–21)	6 (3–13)	– 0.934≠	0.351	NS
	Range	3–32	3–30			
OS (months)	Median (IQR)	21 (14–28)	13 (10–19)	– 2.936≠	0.003	HS
	Range	11–32	3–30			

with the size of nodules as prognostic factors like *Lai et al* [30] who suggested that the combination of the total tumor diameter ≤ 8 cm and an AFP level ≤ 400 ng/mL would result in favorable survival outcomes. The 5-year DFS rate was 74.4%.

Others used the AFP level in combination with the number of nodules to assess the outcome after locoregional treatment, like *Shin et al.* [31], who found that tumor size (≤ 5 cm) and single nodularity were predictive factors for CR, and multi-nodularity and elevated levels of AFP (> 20 ng/mL) were predictive factors for recurrence after CR in patients who underwent TACE as a first-line therapy. Another study of 357 patients with HCC who underwent radiofrequency ablation for primary HCC between 2001 and 2013 showed that male sex, AFP level (> 10 mg/mL), and multiple tumors were significantly correlated with a high rate of HCC recurrence after complete ablation [32].

The AFP model was used to predict recurrence after liver transplantation for patients with HCC. In general, recurrence was higher in high-risk patients than in low-risk patients. It was found that among 432 patients fulfilling the Milan criteria, the 5-year risk of recurrence was 12.8% in patients with a low-risk AFP model and 32.4% in patients with a high-risk AFP model. In the same study, of 142 patients beyond the Milan criteria, the risk of recurrence was 14.9% among patients with a low-risk AFP model and 58.9% in patients with a high-risk AFP model [13]. Further, another study assessed the AFP model as a predictor of recurrence in patients with HCC who underwent liver transplantation and found that low-risk patients showed 21.1% of 5-year recurrence rate, which was lower than that of high-risk patients who showed 57.7% of 5-year recurrence rate [33].

To our knowledge, no study evaluated the AFP model as a prognostic model for patients undergoing locoregional treatment for HCC. In the current study, we used the AFP model with its components: AFP level in combination with the size of the largest nodule and the number of nodules as a prognostic model for predicting response, recurrence, and survival in patients with HCC after TACE. In the current study, in low-risk patients according to the AFP model, recurrence was lower (71.2%) than in the high-risk group (78.2%). When we classified the cases, who underwent TACE with AFP level < 100 IU/mL according to the AFP model, recurrence was less in the low-risk group (37 patients (71.2%)) than it was in the high-risk group (13 patients (81.2%)). *Jinsoo et al.* also assessed the AFP model as predictor of survival in patients with HCC who underwent liver transplantation and found that low-risk patients had a 5-year survival rate higher than that of high-risk patients (76.2% vs. 52.2%, respectively) [33]. In our patients, the 3-year survival in the low-risk group was higher than that in the high-risk group (37.3% vs. 11.6%, respectively). Our study is the first that has tried to predict the response, recurrence, and survival after TACE depending on three parameters (level of AFP, number of nodules, and size of largest nodule collectively) in the form of the AFP model, which was recently validated for patients with HCC undergoing liver transplantation by the French group [10]. More studies are still needed with larger sample sizes to validate its use. Further comparative studies between the AFP model and other prognostic scores for patients with HCC who will perform TACE are needed to figure out the best predictors of response, recurrence, and survival. Further prospective studies are still needed on the efficacy of the AFP model in predicting recurrence and survival in patients with vascular invasion who are candidates for locoregional treatment.

Conclusion

The AFP model may have a prognostic value as a predictor of response, recurrence, and survival in patients with HCC undergoing TACE, especially in patients with AFP levels less than 100 IU/mL; however, more studies with larger sample sizes are needed to validate its use. We may recommend a strict program and shorter periods for follow-up for high-risk groups for TACE according to the AFP model as they may have a worse prognosis (in the term of response, recurrence, and survival) than low-risk groups.

Abbreviations

HCC: Hepatocellular carcinoma; AFP: Alpha-fetoprotein; TACE: Trans arterial chemoembolization; mRECIST: Modified response evaluation criteria in solid tumors; CR: Complete response; PR: Partial response; SD: Stationary disease; PD: Progressive disease; OS: Overall survival; DFS: Disease-free survival.

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Authors' contributions

ME designed and coordinated the study; ME and HMA analyzed the data; ME and MAA interpreted the data; ME and SA wrote the manuscript; ME and MKS revised the article; all authors approved the final version of the article.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

The study was approved by the Research and Ethical Committee of Faculty of Medicine, Ain Shams University, Cairo, Egypt in accordance with local research governance requirements (FMASU R 66/2021).

Consent for publication

Not applicable

Competing interests

All authors declare that there are no conflicts of interest that could have appeared to influence the work reported in this paper.

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