Pretransplantation α-fetoprotein level as a predictor of hepatocellular carcinoma recurrence after adult living donor liver transplantation within milan criteria in egyptian patients

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Received 21 November 2018
Accepted 22 December 2018

The Egyptian Journal of Internal Medicine 2019, 31:203–207

Background and aim of the work
Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world and the third most common cause of mortality in patients with cancer. HCC represents one of cirrhosis complications. The aim of this study was to assess pretransplantation α-fetoprotein (AFP) level as a predictor for HCC recurrence after living donor liver transplantation (LDLT).
Patients and methods
This is a cross-sectional retrospective study for patients with HCC who underwent LDLT and within Milan criteria. Preoperative assessment was performed to assess etiology, operability, and AFP. Locoregional therapy was performed preoperatively as a bridge therapy or for downstaging in patients beyond the Milan criteria. Postoperative abdominal ultrasound and AFP measurement have been performed for HCC recurrence surveillance, as routine investigations. If there is a suspicious lesion of HCC recurrence, triphasic computed tomographic scan is performed and biopsy may be performed.
Results
Data of 75 patients with HCC who underwent LDLT were analyzed retrospectively. Seventy-three patients were infected with hepatitis C virus; two of them were previously infected with hepatitis B virus, one patient with hepatitis B virus infection, and one patient had hepatitis C virus/hepatitis B virus coinfection. AFP may predict HCC recurrence after LDLT (area under the curve=0.806) at cutoff value of more than 66 ng/ml, with 60% sensitivity, 94.3% specificity, 42.9% positive predictive value, and 97.1% negative predictive value.
Conclusion
Preoperative serum AFP level may predict post-transplant HCC recurrence. It may be used in combination with other factors to create a prognostic model that may predict HCC recurrence after liver transplantation.

Keywords:
α-fetoprotein, hepatocellular carcinoma, histopathology, liver transplantation, recurrence

Egypt J Intern Med 31:203–207

1110-7782

Introduction

Hepatocellular carcinoma (HCC) is one of the primary liver malignant tumors [1]. It is the sixth most common cancer worldwide, contributing toward 5.6% of new cases diagnosed totally [2]. HCC is the third cause of cancer-related death worldwide [3] and is considered currently as the main cause of death in patients with cirrhosis with hepatitis C virus (HCV) [4].

In the past decade, there was approximately a two-fold increase in HCC proportion among patients with chronic liver disease in Egypt [4].

Patients with increase risk of HCC development should be included in screening programs by liver ultrasonography, with or without α-fetoprotein (AFP), every 6 months [5]. AFP is a serological marker that is commonly used to detect HCC; however, it is not accurate owing to low sensitivity and specificity [6].

Orthotopic liver transplantation (OLT) is the best available treatment modality for HCC which goes beyond criteria of surgical resection and within Milan criteria [5]. Patients within the Milan criteria and who undergo OLT have an estimated 5-year recurrence-free survival rate of nearly 83% [7].

The aim of this study was to assess pretransplantation AFP level as a predictor for HCC recurrence after living donor liver transplantation (LDLT).

Patient and methods

This is a cross-sectional retrospective study for patients with HCC who underwent LDLT by Ain Shams University team between April 2008 and December 2016. Follow-up period was from 11 to 94 months. The scientific and ethical committee of Ain Shams University approved the study protocol. All patients signed a written informed consent prior to inclusion into this study.

Preoperative assessment

HCC was diagnosed preoperatively in all patients by abdominal ultrasound and/or serum AFP, and diagnosis was confirmed by HCC radiological hallmarks using dynamic multidetector computed tomography (CT) or MRI.

Milan criteria were applied as a basis for selecting patients with cirrhosis and HCC for liver transplantation (LT) (single tumor that was 5 cm or less in diameter or no more than three nodules each 3 cm or less in diameter, if multiple tumors) and no evidence of vascular invasion or distant metastases. Locoregional therapy (LRT) was performed preoperatively as a bridge therapy or for downstaging in patients beyond the Milan criteria.

All patients were subjected to history taking and complete physical examination, laboratory investigations (complete blood count, aspartate aminotransferase, alanine aminotransferase, total and direct bilirubin, serum albumin, blood urea nitrogen, Creatinine, international normalized ratio, viral marker, for example, hepatitis B surface antigen, HCV antibody, and AFP level at the time of list placement and after LRT) and radiological imaging (CT chest and bone scan).

Postoperative assessment

After OLT, histopathological examination was done to explants to assess the presence of incidental tumor, number of nodules, size of the largest nodule, and degree of differentiation. Abdominal ultrasound was done every 1 month for 6 months then every 3 months for 1 year then every 6 months, and AFP measurements have been performed every 6 months for HCC recurrence surveillance, as a routine service. If there is a suspicious lesion of HCC recurrence, CT triphasic is performed, and biopsy may be performed.

Statistical analysis

Data were collected, revised, coded, and entered to the statistical package for social science (version 20; IBM Corp., Armonk, New York, USA). Qualitative data were presented as frequency and percentages. Quantitative variables were presented as mean±SD. Comparison of qualitative data between groups was performed using χ^2-test or Fisher's exact test. Independent t-test was used to compare quantitative data between groups with parametric distribution whereas Mann–Whitney test was used to compare quantitative data with nonparametric distribution. Logistic regression analysis was used to assess predictors of recurrence. Receiver operating characteristic curve was used to assess the ability of pretransplantation AFP as a prognostic factor to predict HCC recurrence after LDLT. A P value of less than 0.05 was considered statistically significant.

Results

Data of consecutive 75 patients with HCC who underwent LDLT were analyzed retrospectively. Seventy patients were male and five patients were female, with mean age of 53.52±6.80 years (range from 34 to 67 years). Seventy-three patients were infected with HCV; two of them were previously infected with hepatitis B virus (HBV) (hepatitis B surface antigen-negative, hepatitis B surface antibody-positive and hepatitis B core antibody-positive), one patient with HBV infection, and one patient had HCV/HBV coinfection. The mean of Model For End-Stage Liver Disease Score was 15.11±5.17 (ranged from 7 to 31). Nine patients were classified as Child A, 35 as Child B, and 31 as Child C. Laboratory profiles of the patients are described in Table 1.

Forty-three patients underwent LRT before transplantation as bridging therapy (31 patients) or

Table 1 The mean and interquartile range of pretransplantation laboratory data

	Mean±SD/median (IQR)*	Range
WBC	5.12±2.62	1.6–15.9
HB	11.05±1.87	7.9–16
PLT	70.85±38.11	14–253
AST	68 (47–114)*	21–527
ALT	44 (28–83)*	13–673
T bil	2.9 (1.6–4.8)*	0.5–16
D bil	1.3 (0.6–2.5)*	0.2–8
Alb	2.62±0.57	1.4–4.4
INR	1.62±0.43	1.1–3.8
ALP	118.19±76.29	18–527
GGT	51 (24–117)*	8–673
BUN	15.31±6.14	5–33
CR	0.95±0.36	0.5–2.9
AFP	9.5 (5.3–30.5)*	1.3–325

AFP, α-fetoprotein; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CR, creatinine ratio; D bil, direct bilirubin; GGT, γ-glutamyltransferase; HB, hemoglobin; INR, international normalized ratio; IQR, interquartile range; PLT, platelet; T bil, total bilirubin; WBC, white blood cell. *IQR= Interquartile range.

for downstaging of tumor (12 patients). Types of LRTs are illustrated in Fig. 1.

From 75 patients with HCC in our study, there were five patients who had recurrent HCC after transplantation. The main sites of recurrence were the liver (two patients), liver and lungs (one patient), liver and lung with lymph nodes involvement (one patient), and multiple sites (one patient).

There were statistically significant differences between patients with recurrent HCC and those who had no recurrence regarding pretransplantation aspartate aminotransferase and AFP results. Regarding age and other pretransplantation laboratory data, there were no statistically significant differences between the two groups (Table 2). There was a highly significant positive correlation between number of malignant nodules in explants and HCC recurrence (r=0.456, P<0.001) (Table 3).

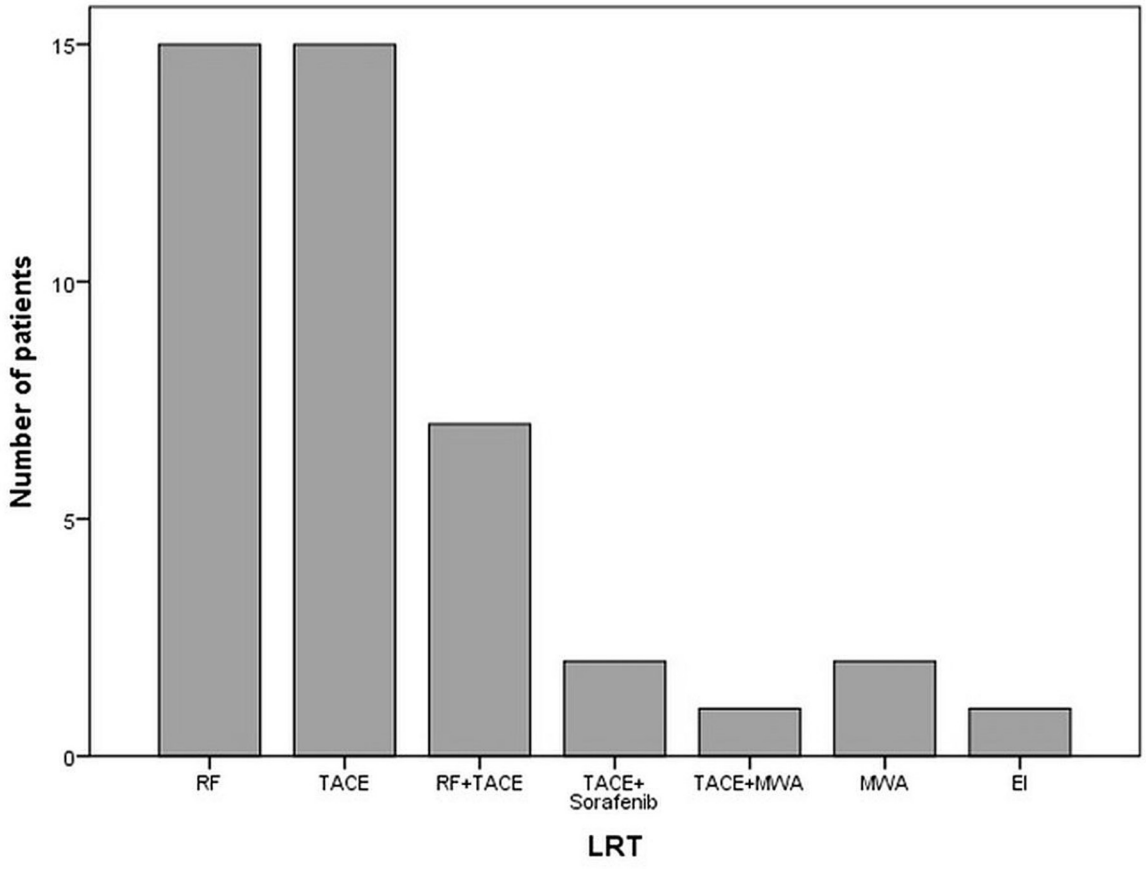
It seems from the receiver operating characteristic curve that AFP may predict HCC recurrence after LDLT (area under the curve=0.806) at cutoff value of more than 66 ng/ml, with 60% sensitivity, 94.3%

Table 2 Comparison of two groups regarding age and pretransplantation laboratory data

Variables	No recurrence (*N*=70)	Recurrence (*N*=5)	*P* value
Age	53.49±6.73	54.00±8.60	0.872
WBC	5.13±2.69	4.86±1.52	0.823
HB	11.01±1.90	11.58±1.30	0.515
PLT	70.33±37.83	78.20±45.96	0.659
AST	63.5 (47–112)	158 (79–319)	0.024*
ALT	44 (28–81)	117 (69–164)	0.111
T bil	2.9 (1.6–4.8)	2 (1.8–3.6)	0.581
D bil	1.35 (0.6–2.5)	0.8 (0.5–2)	0.524
Alb	2.63±0.58	2.40±0.31	0.384
INR	1.61±0.43	1.71±0.33	0.611
ALP	120.97±77.87	79.20±32.24	0.239
GGT	51.5 (23–118)	43 (35–52)	0.603
BUN	15.16±5.94	17.40±9.13	0.434
CR	0.95±0.37	0.96±0.31	0.953
AFP	9.15 (4.8–25)	84.6 (14.8–214)	0.023*

AFP, α-fetoprotein; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CR, creatinine ratio; D bil, direct bilirubin; GGT, γ-glutamyltransferase; HB, hemoglobin; INR, international normalized ratio; PLT, platelet; T bil, total bilirubin; WBC, white blood cell. *Statistically significant.

Figure 1



LRT that performed pretransplantation as a bridge therapy or for downstaging. EI, ethanol injection; LRT, locoregional therapy; MWA, microwave ablation; RF, radiofrequency; TACE, transarterial chemoembolization.

specificity, 42.9% positive predictive value, and 97.1% negative predictive value (Fig. 2).

Discussion

HCC is one of the major reasons for LT, and prevention of HCC recurrence is important to improve the long-term survival of patients with HCC after LT [8]. Revealing factors associated with tumor recurrence after LT will be valuable in predicting prognosis and to guide optimal therapy. There is a need for preoperative, simple, and cheap test as a predictor of HCC recurrence after LT.

Table 3 Group comparison regarding the number of nodules in explants

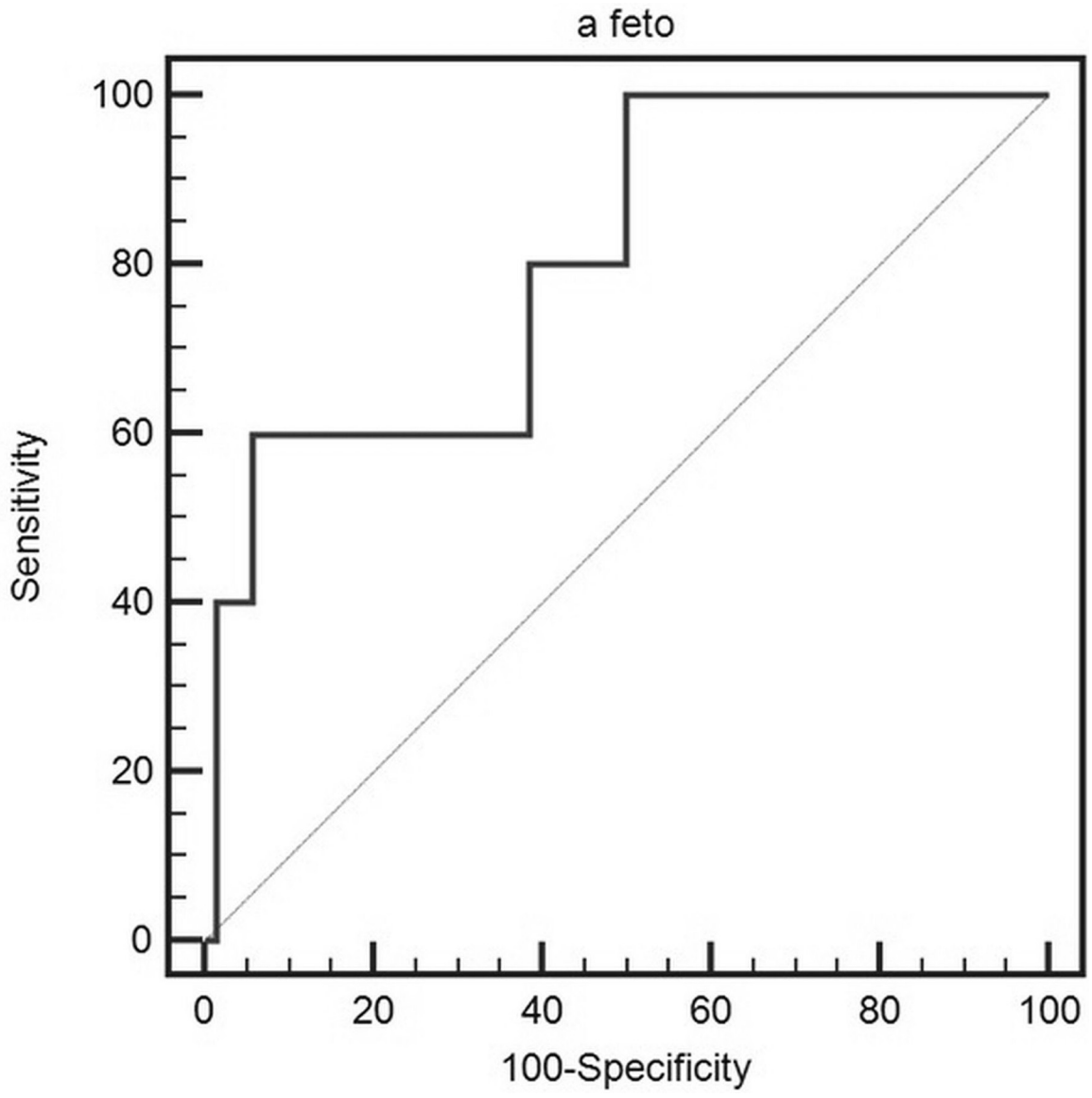
Number of nodules	No recurrence [*n* (%)]	Recurrence [*n* (%)]	*P*
≤3 nodules	66 (94.3)	2 (40)	0.005*
>3 nodules	4 (5.7)	3 (60)	

*Statistically significant.

The reported recurrence rates range from 3 to 26% [7,9–11]. In our study, HCC recurrence after LDLT was diagnosed in 6% of patients. This difference may be assumed to the use of different criteria other than Milan criteria for selection HCC patients for LT.

In this study, pretransplantation AFP was associated with increased risk of HCC recurrence after LDLT with value of more than 66 ng/ml in patients with HCC within Milan criteria. Such an association has

Figure 2



Receiver operating characteristic curve showing sensitivity and specificity of α-fetoprotein in hepatocellular carcinoma recurrence after living donor liver transplantation.

been found in many previous studies, especially when AFP levels were greater than 1000 ng/ml before OLT [12,13]. However, lower significant AFP values have shown a positive association with HCC relapse.

Figueras *et al*. [14] pointed out that pretransplant AFP more than 300 ng/ml was associated with HCC recurrence after LT. Other study reported that pretransplantation AFP levels more than 200 ng/ml led to increased HCC recurrence [15]. Perez-Saborido *et al*. [16] described that HCC recurrences were more common in patients with AFP more than 200 ng/ml, in comparison with those with AFP less than 200 ng/ml (37.5 vs. 13.3%), but this was statistically insignificant (P=0.08).

Xu *et al*. [8] divided patients into three groups by AFP level (<20, 20–400, and >400 ng/ml) and found tumor recurrence rates was significantly high if AFP was more than 400, which is the same result reached later by other study [17].

This difference between studies may be owing to differences in study structure, different selection criteria for transplantation, intervention before transplantation, vascular invasions, the number of nodules in explants, and the presence of satellite nodules.

Recently, AFP was incorporated in many scoring models that can predict the risk of HCC recurrence after LT [18,19].

Although many reviews consider only AFP values above 1000 ng/ml significant for HCC recurrence, our study raises the alert that lower values of AFP should also be placed under scope of researchers, especially if AFP will be used as a part of prognostic models.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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