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Diagnostic and Prognostic Role of α-Fetoprotein in Hepatocellular Carcinoma: Both or Neither?

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BACKGROUND: The clinical usefulness of α-fetoprotein (AFP) in hepatocellular carcinoma (HCC) management is debatable.

OBJECTIVES: To assess, in a large multi-centric survey, diagnostic and prognostic reliability of AFP, predictive factors, and any correlation with the tumor immunophenotype.

METHODS: A total of 1,158 patients with HCC were analyzed with reference to serum AFP levels at diagnosis. We evaluated: HCC grading, histotype, and size; Okuda, tumor–nodes–metastases (TNM), and Child-Pugh scores; liver function, symptoms, presence of metastases or portal thrombosis, etiology, survival, and treatment. In 66 patients with histological diagnosis, the pathologists evaluated p53 overexpression, MIB 1 labeling index, BCL-2 positive cells (index of apoptosis), and CD44 (adhesion molecule) positivity.

RESULTS: Patients were divided into three AFP groups: normal (<20 ng/mL) [46%], elevated (21–400 ng/mL) [36%], and diagnostic (>400 ng/mL) [18%]. Statistical correlations were significant for: weight loss ($p = 0.0056$), pain ($p = 0.0025$), Child-Pugh score ($p = 0.001$), tumor size, Okuda's and TNM stages, metastases, thrombosis, type of treatment (all $p < 0.0001$), and female sex ($p < 0.004$). AFP correlated with survival overall, in patients untreated, transplanted, or undergoing locoregional treatments; but not in those surgically treated. In the discriminant analysis, the related variables were size, female sex, Child-Pugh score, TNM staging (steps 1–4). When using the receiver operating characteristic curve, the prognostic reliability of AFP was limited with area under the curve of 0.59. Finally, patients with low expression of BCL2 had high AFP levels ($p < 0.05$). AFP positively correlated with Edmonson score ($p < 0.0001$).

CONCLUSION: The evaluation of this large series of HCC patients allowed us to: confirm the low sensitivity (54%) of AFP in the diagnosis of HCC and its prognostic value, albeit limited, being tumor size, female sex (intriguingly enough), Child-Pugh score, and TNM staging independent predictors.

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BACKGROUND

α-Fetoprotein (AFP) was discovered in 1963 by Abelev and ever since utilized in the surveillance of patients with cirrhosis and in the diagnosis of hepatocellular carcinoma (HCC) as well as of gonadal carcinoma (1), with erratic report of positivity of the marker in gastric (2), lung cancer (3), or even more rarely, in other type of cancers. Throughout these 40 years, the levels of sensitivity and specificity of the marker

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have been widely described and discussed (4–9), particularly with respect to its efficiency in surveillance protocols in cirrhotics for the development of HCC. The European Association for the Study of the Liver (10) in 2001 and the Italian Association Study of the Liver (AISF, Hepatocellular Carcinoma, Guidelines for Diagnosis and Treatment, 2001 (11)), in drawing their guidelines on the management of HCC stated, with a slightly different degree of certainty, that even though the markers actually lacks sensitivity and specificity, still it should be used for screening purposes in the population at risk of cirrhotics, in association with ultrasound examination, in surveillance programs. Despite what above, there are strongly dissonant voices with an "obituary" of AFP, having been published in 2001 in the *Journal of Hepatology* (12). Those who do not agree with that standpoint counteract by saying that, even though lacking sensitivity, AFP, when presenting levels constantly above the normal range or particularly when showing a steady increase, identifies a subpopulation of cirrhotics at high risk of HCC development (13).

While the scientific literature is crowded by reports on the sensitivity and specificity of AFP and on the factors that may modulate its levels (14–16), a comprehensive large-scale study with a global reappraisal on the diagnostic and prognostic role of AFP and on the clinical, morphological, and biological factors determining its levels in a series of patients of clear numerical relevance is still lacking.

The purpose of this study, based on a partly retrospective, partly prospective multicenter data collection, carried out by the ITALICA group over a consecutive series of more than 1,000 HCC patients, was in fact to fill this empty space.

PATIENTS

A total of 1,158 consecutive HCC patients (874 males, 284 females, M/F ratio 3/1, mean age 64 in males, 67 in females) recruited from January 1986 to December 2001 in seven clinical institutions entered the study. The diagnosis was histologically confirmed in 459 (39%). In the remaining patients, the diagnosis was obtained according to unequivocal clinical and imaging data (Ultrasonic CT scanning) and the follow-up until year 2000; after this year the European Association for the Study of the Liver (EASL) criteria were utilized, that is the concordance of two imaging procedures among Spiral CT, NMR with paramagnetic contrast injection or ultrasound with second generation intravenous contrast (Sonovue, Bracco, Italy) confirming the presence of a lesion characterized by early arterial enhancement or increased AFP levels with one imaging procedure. Tumor size and number were determined on the bases of the imaging procedure performed, with special reference to the diameter of the largest lesion diagnosed if multiple nodules were present. Tumor stage was determined according to the Okuda, tumor–nodes–metastases (TNM) staging systems and, as in previous ITALICA reports (17, 18) as: solitary nodular, paucifocal (2–3 nodules), multifocal (>3 nodules), diffuse, and massive type. The Cancer of the Liver Italian Program (CLIP) staging was not considered, since it includes AFP as a staging criteria (19) and the Barcelona Clinic Liver Cancer (BCLC) (20) system was not so widely diffused when the data collection started and was not recorded. Status with respect to hepatitis B virus (HBV) and hepatitis C virus (HCV) infection was determined on the basis of HBsAg, HBsAb, HBcAb, HbeAg, HbeAb, anti-HCV, and anti-HDV using commercially available immunoassay kits (EIA; Abbott Diagnostics, North Chicago, IL, USA). Alcohol abuse was determined as the long-lasting consumption of more than 80 g ETOH/day in males and 40 g in females. Liver function tests (AST, ALT, γGT, FA, albumin, bilirubin, prothrombin time, and platelets) were recorded, as well the Child-Pugh risk group and score and the presence of relevant symptoms (ascites, jaundice, abdominal pain, weight loss, as well as the demonstration of portal thrombosis, extra hepatic metastases, or associated nonhepatic disease). First treatment indication after diagnosis and association of different treatments were recorded together with survival.

AFP levels were determined by immunoenzymatic chemiluminescence and stratified for statistical purposes in Normal (within the normal range of 20 ng/mL), Elevated (above normal range up to 400 ng/dL), and Diagnostic (above 400 ng/dL). The cutoff for normal AFP levels (20 ng/mL) was chosen on the bases of the EASL guidelines (10) plus on the data reported in the majority of the studies on the topic. In all the patients in whom the diagnosis was histologically confirmed on the bases of a fine needle aspiration biopsy, grading according to Edmonson (well, moderately, or poorly differentiated), and hystotype (trabecular, adenoid, mixed, hepatocholangiocellular, fibrolamellar, scirrous) entered the data sheet. In a subgroup of 66 consecutive patients, diagnosed in our unit, we additionally evaluated:

- cytoroliferation rate, by using the MIB1 Ki67 monoclonal antibody (Immunotech, France) We used a semiquantitative score in dividing HCC samples with less than 1% positive cell in at least 10 high power fields (HPF), between 1% and 10% and above 10%;
- apoptosis, indirectly by determining the percentage of Bcl2 positive cells (Bcl2clone 124, DAKO, Denmark);
- p53 protein hyper-expression (anti-p53 monoclonal antibody, DO-1, IgG2, Immunotech, France), as a marker of p53 gene mutation;
- CD44 expression, adhesion molecule that, when mutated plays a role in cell proliferation and cell invasive properties (CD44 std; Bender Medysistem).

This with the aim of identify a possible relationship between biological parameters and the level of the marker that could be on the basis of a possible biologic role of AFP in hepatocarcinogenesis.

Statistics was based on Student's t-test, χ^2, multiple regression analysis, and discriminant analysis according to the forward stepwise model on the variables turning out as significant in the simple regression analysis, when appropriated. Survival curves were calculated by Kaplan–Meier and

Table 1. Etiology of Liver Disease

	Etiology	
	Male (%)	Female (%)
HBV	10.7	10.9
HCV	49.8	48.4
Alcohol	11.7	14.10
HBV + HCV	4.4	4.3
Other*	23.4	22.3

*HBV + alcohol, HCV + alcohol, primary biliary cirrhosis and primary sclerosing cholangitis, Wilson's disease, hemochromatosis.

log-rank test (according to Wilcoxon–Breslow). p Levels lower than 0.05 were considered as significant. A receiver operating characteristic (ROC) curve for AFP levels with respect to survival, subgrouping the patients in "short" and "long" survivors (those surviving less and longer than the median survival (19 months), respectively) was also performed.

RESULTS

The distribution of the patients with respect to the etiology of the disease is reported in Table 1. There were basically no difference between males and females: both in male and female patients, almost 50% of cases are related to HCV infection, with more than other 10% of cases with association between HCV and ethanol, and an additional 4% of cases in which HCV was associated to HBV, making up to about 65% of cases in some way related to HCV infection.

AFP levels were within normal range in 46% of the cases, between normal range and diagnostic levels (21 to 400 ng/mL) in 36% and above 400 ng/dL in 18%. In looking for a possible additional clinical differences, according to the Italian guidelines that consider 200 ng/mL as the diagnostic level (11), we also subgrouped the patients in four tiers (<20, 21–200, 201–400, and >400 ng/mL) but only 66 patients (6%) entered the category included between 200 and 400 ng/mL and, for sake of simplicity, only three tiers were considered.

The levels of the marker stratified for tumor size are described in Table 2. Basically, a diagnostic AFP level was reached in 7% of patients with tumor size below 2 cm and in 30% of those with tumors exceeding 5 cm ($p < 0.0001$). Similarly, a statistically significant correlation was observed with respect to tumor focality (Table 3) and staging according to TNM ($p < 0.0001$) (Table 4) and Okuda ($p < 0.0001$) (Table 5). The presence of portal thrombosis was significantly associated with high AFP levels ($p < 0.0001$) and the same was true for the presence of extra-hepatic metastasis ($p < 0.0001$ by χ^2).

Table 2. AFP Levels According to Tumor Size ($p < 0.0001$)

		AFP Level		
Tumor size	N	<20 ng/mL	21–400 ng/mL	>400 ng/mL
<2 cm	223	120 (54%)	86 (38.5%)	17 (7.5%)
2–3 cm	279	142 (51%)	108 (39.5%)	29 (9.5%)
3–5 cm	320	134 (42%)	129 (40%)	57 (18%)
>5 cm	185	81 (44%)	49 (26%)	55 (30%)

Table 3. AFP Levels According to Focality of Lesions ($p < 0.0001$)

		AFP level		
Focality	N	<20 ng/mL	21–400 ng/mL	>400 ng/mL
Single	520	267 (51%)	200 (38.5%)	53 (10.5%)
Paucifocal (2–3 nodules)	248	109 (44%)	100 (40%)	39 (16%)
Multifocal (>3 nodules)	205	81 (39.5%)	69 (33.5%)	55 (27%)
Diffuse	97	35 (36%)	27 (28%)	35 (36%)
Massive	35	12 (34.5%)	3 (8.5%)	20 (57%)

The levels of AFP were higher in patients with weight loss ($p < 0.0056$) and abdominal pain ($p < 0.0025$). AFP levels above 400 ng/mL were characteristics of patients with less differentiated (G3) HCC (according to Edmonson scoring system) ($p < 0.0001$). No significant correlations were documented with "so-called" liver function tests or with disease etiology. Females had significantly higher levels of the marker ($p = 0.004$) We searched for potential confoundings for this association between female sex and high AFP levels with respect to tumor size, Child-Pugh score, etiology, and staging but there were not significant differences between male and female patients (16).

About 31% of the patients did not undergo any type of treatment or were treated with hormonal treatment (tamoxifen), that we consider by now largely ineffective in HCC treatment (21, 22). Eleven percent of the patients underwent a radical treatment (surgical resection or orthotopic liver transplantation) while a large share (49%) underwent locoregional treatments such as percutaneous ethanol injection (PEI-21%) or lipiodol-mediated transarterial chemoembolization (TACE-30%). The percentage of patients with high AFP that did not undergo any treatment (55%) was significantly higher than that of patients with AFP lower than that limit (34%, $p < 0.0001$) (Table 6).

A 60% of patients were subgrouped as Child-Pugh A, 31% as B, and 9% as C. Patients in the Child-Pugh C risk group were characterized by significantly higher AFP levels ($p < 0.001$).

Table 4. AFP Levels According to TNM Stage ($p < 0.0001$)

		AFP Levels		
	N	<20 ng/mL	21–400 ng/mL	>400 ng/mL
TNM I	95	51 (53.5%)	41 (43.5%)	3 (3%)
TNM II	265	122 (46%)	106 (40%)	37 (14%)
TNM III	269	98 (36.5%)	103 (38.5%)	68 (25%)
TNM IV	58	24 (41.5%)	14 (24%)	20 (34.5%)

Table 5. AFP Levels According to Okuda Stage ($p < 0.0001$)

		AFP Levels		
Okuda Stage	N	<20 ng/mL	21–400 ng/mL	>400 ng/mL
1	656	314 (48%)	243 (37%)	99 (15%)
2	341	152 (44.5%)	104 (30.5%)	85 (25%)
3	61	17 (28%)	15 (24.5%)	29 (47.5%)

With respect to survival analysis, patients with normal AFP levels showed a median survival three times higher than that of patients with diagnostic AFP (Fig. 1). Same significant differences were observed when HCC patients were subgrouped into treated or untreated (Figs. 2 and 3) and among those treated, similar results were observed in those surgically treated ($p < 0.05$), or treated by PEI ($p < 0.001$) or TACE ($p < 0.002$). When surgical patients were subgrouped according to the type of surgery (OLTx or resection), AFP showed a prognostic role only in those who underwent to OLTx ($p = 0.03$), while this was not confirmed in those who underwent surgical resection ($p = 0.3$). However, only nine patients with AFP levels above 400 underwent surgery and this may justify the lack of a significant difference.

The prognostic role of AFP levels was additionally confirmed by an internal validation in the homogenous subgroups of patients (263 patients, 24%) with single small tumors <3 cm in Child-Pugh A risk group ($p < 0.05$).

By using the discriminate forward stepwise analysis, the parameters included as independent predictor of increased AFP levels were tumor size, female sex, Child-Pugh risk group, TNM staging, in this order (steps 1–4).

We finally carried out a ROC curve of AFP levels with respect to median survival. The cut off chosen with the statistical package (Statdirect) was of 600 ng/mL, this point presenting a sensitivity of 23% and a specificity of 93%. The area under the curve (AUC) was of 0.59 (Fig. 4). Similar data were obtained when we tested also tumor size with ROC curve with respect to survival, with an AUC of 0.61.

With respect to the subgroup of the 66 patients that were examined from the immune-phenotypic point of view, the only correlation found was an inverse one between AFP and degree of expression of Bcl2 ($p < 0.05$). Not significant correlation emerged with CD44, p53, and Ki67 (Table 7).

Table 6. Treatment According to AFP Levels

	AFP Levels	
Treatment	<400 ng/mL	>400 ng/mL
Untreated	218 (34%)	253 (55%)
Surgery	64 (10%)	23 (5%)
OLTx	19 (3%)	5 (1%)
PEI	128 (20%)	46 (10%)
TACE	210 (33%)	133 (29%)

DISCUSSION

Forty years have been spent in discussing the role of AFP determination in the management of HCC but the debate is still open. The scientific societies' guidelines still support its use for surveillance purposes in patients with cirrhosis but part of the scientific community strongly argues against this statement. In which patients AFP levels tend to be elevated is also debated and it has been suggested, for instance, that patients with HBV infection-related liver disease are characterized by higher AFP levels (15).

This study is not an original one but, given the size of the sample included, is to the best of our knowledge the largest reported so far taking into consideration so many different factors and allows therefore a number of consideration that could be considered as conclusive.

AFP Diagnostic Role

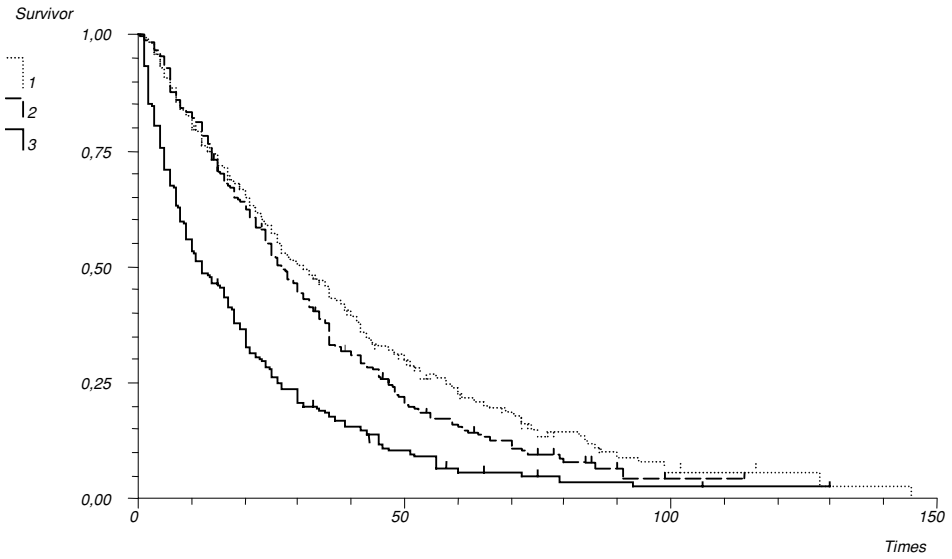
The sensitivity of marker for the most used cutoff value (20 ng/mL), according the data from our survey is only 54%. Diagnostic values are observed only in 18% of the subjects. Even if we consider levels included between 21 and 400 ng/mL as an indication of HCC presence, than we will still miss about 50% of HCC cases. Conversely, among the 54% of patients with HCC and abnormal levels of AFP (>20 ng/mL), only a final figure of 25% are diagnosed at an "early" stage (single tumor less than 5 cm or up to three nodules less than 3 cm) and may undergo radical treatment. If we consider instead the diagnostic value of AFP above 400 ng/mL, it would be useful for early diagnosis and for therapeutic purpose only in 10% of patients. If we stick to a stricter definition of early disease and consider as harboring "early" HCC only the patients with single node smaller than 2 cm, than the percentage of cases in which AFP is diagnostic is 7%.

The above observations rule out the use of AFP from the diagnostic approach to primary liver cancer.

Even though our study was not designed to investigate the role of AFP in HCC screening or in identifying patients at risk, the large number of false negative results and the high number of false positive reported in the literature (4), seem to rule out the use of AFP not only in the diagnosis, but also for screening purposes or in identifying the patients at "higher risk" for HCC: AFP could be evaluated only for the initial screening and, if negative at screening at time 0, not used in the subsequent surveillance of the cohort of cirrhotic patients, as already claimed (11) and despite previous cost-effectiveness analyses (23, 24).

AFP and Tumor Staging

The percentage of patients with increased AFP tends to increase with tumor size and patients with tumors above 5 cm have in 30.5% and 26.5% values of the marker in the alarm or diagnostic range, respectively. This also means, however, that 43% of the patients with advanced HCC have still AFP levels within the normal range, thus suggesting that a normal results in the determination of the marker does not mean HCC is not



	AFP	MEDIAN (Months)
1	<20 ng/ml	31
2	21-400 ng/ml	27
3	>400 ng/ml	12

Figure 1. Global survival according to AFP levels ($p < 0.0001$).

there, but does not even mean that if it is there, it is at least in its early stages. Very similar consideration can be made with respect to tumor stage, particularly in terms of TNM. With regards to Okuda stage (that considers tumor size and liver function, both statistically correlated with AFP levels) in our series, this corresponds better with AFP levels; in fact, the percentage of patients with advanced Okuda stage (III) and normal levels of the marker is relatively small (28%). Again, the usefulness of AFP in patients with untreatable disease is debatable.

Also, when the focality of the tumor was considered (monofocal, paucifocal, multifocal, diffuse, and massive) patients with diffuse and massive HCC had increased levels of the marker in 36% and 59% of the cases, respectively. Despite what above a clear-cut increase in AFP may or may not indicate the presence of large, diffuse or massive HCC.

Finally, significantly higher AFP levels were documented in patients with either portal thrombosis or extra-hepatic secundaries, as previously reported by others.

AFP and Liver Disease Etiology, Activity, Stage, Patients' Demography, and Treatment

Despite what previously reported in the literature (14–16) and despite the fact that patients with viral etiology tended to have higher level of the marker, we could not detect any significant relationship between AFP levels and disease etiology. As said, patients with poor liver function had significantly higher AFP, while no correlation whatsoever was found with transaminases, γ-glutamyl transferase, alkaline phosphatase, albumin or prothrombin time, when singularly considered.

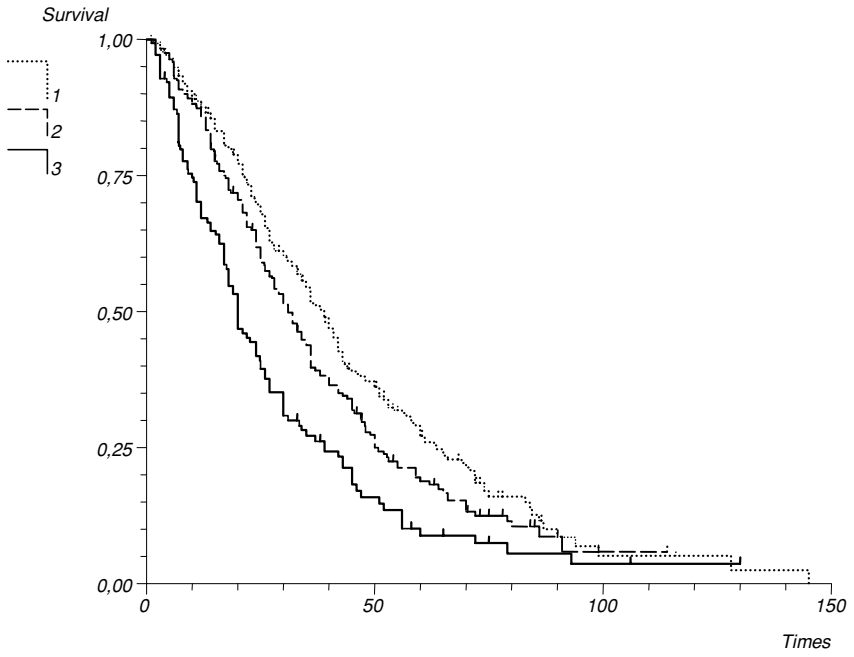
No correlation with the patients' age was detected, while females had significantly higher levels of the marker. This may obviously be a correlation documented purely by chance but for the fact that there is a previous observation confirming our findings, which are in any case hard to explain (16). In this study, no difference emerged between male and female from any other point of view, still female patients shows high level of the marker (>200 ng/mL) more frequently than males.

A little more than half of the patients with AFP levels above 400 ng/mL will not undergo any treatment, while same is true for 34% of patients with levels of the marker below this level. Conversely 65% of patients with normal AFP underwent some type of treatment. Overall the presence of high AFP levels tends to identify patients with poor indication to treatment but does not exclude the possibility of some therapy being performed.

AFP and Tumor Phenotype and Immunophenotype

p53, a commonly mutated gene in HCC, playing a central role in cell-cycle arrest and cell death in response to DNA damage, CD44, cell-surface adhesion glycoprotein indicator of invasive and metastatic behavior (25) and Ki 67 an objective marker reflecting proliferating activity of cells (26) were not significantly related to AFP levels.

Among these immunophenotypical markers, utilized in the subgroup of the 66 patients in whom the study was



	AFP	MEDIAN (Months)
1	<20 ng/ml	39
2	21-400 ng/ml	31
3	>400 ng/ml	20

Figure 2. Survival in treated patients according to AFP levels ($p < 0.0001$).

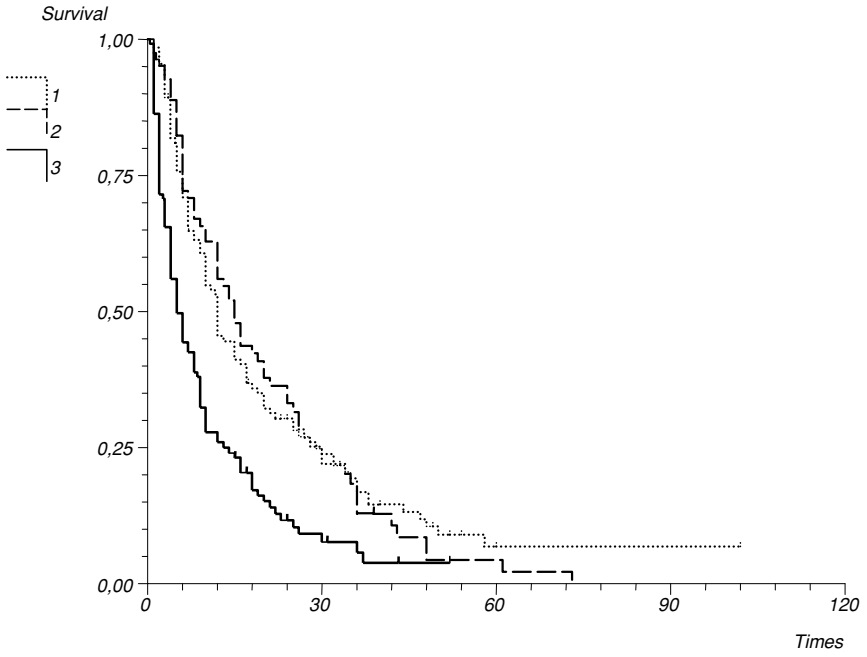
performed, only Bcl-2 expression was inversely correlated with AFP (27–29). BCl-2 plays a main antiapoptotic role and the inverse correlation detected between BCl-2 expression and AFP should be considered as an indication that, at least *in vivo* in HCC, the patients with increased AFP expression, that are characterized by worse prognosis, are characterized by depressed BCl-2 function to which an increased apoptotic cell death should correspond. This is not surprising, since in cancer an imbalance between proliferation and apoptosis is definitely more important than the amount of apoptosis itself and is to be, however, considered in the context of the controversial data published on the relationship between AFP and apoptosis. A recent study (30) has reported that AFP may cause apoptosis in HCC by inducing caspase 3. Also, it has been shown that treatment of hepatoma cells with high levels of AFP may induce BCl-2; thus indicating that in this model apoptosis is not justified by the downregulation of BCL2 itself (31). Both the above data are in contrast with what we found in this series in which an inverse correlation was documented between AFP and intensity of BCL-2 immunostanding. These data and the above hypothesis need both clinical and experimental confirmation.

We obtain no correlation between AFP and cytoproliferation, as expressed by MIB1 Ki67 antibody. Again, *in vitro* experiments have reported a capacity of AFP to give a burst to cell proliferation in embryonal as well as in murin and human hepatoma cell (32, 33). Non-neoplastic cell, on the other hand, do not receive the same stimulus (34), probably due to the lack of specific receptors. Presumably different levels of AFP may play a different role in the regulation of cytoproliferation: according to recent study in fact high levels of AFP >1 mg/mL reduce the proliferation of hepatoma cell line HepG2, while lower level would be a stimulus in the same cell line to cytoproliferation (35). Overall, it is only important to stress that high AFP levels are related to changes in the apoptotic pathway in HCC.

Finally, patients with poorly differentiated tumors were characterized by more frequent finding (31%) of high AFP levels.

AFP and Survival

The best role of the determination of AFP is the definition of the patients' prognosis. This was true in the whole series, remained true when we separated the patients into treated and untreated and even when we stratified them as per type of treatment. The efficiency of AFP was confirmed even when a particularly homogeneous group of early HCC (single nodule <3 cm) in Child A patients was considered ($p < 0.05$). Only



	AFP	MEDIAN (Months)
1	<20 ng/ml	12
2	21-400 ng/ml	15
3	>400 ng/ml	7

Figure 3. Survival in untreated patients according to AFP levels ($p < 0.0001$).

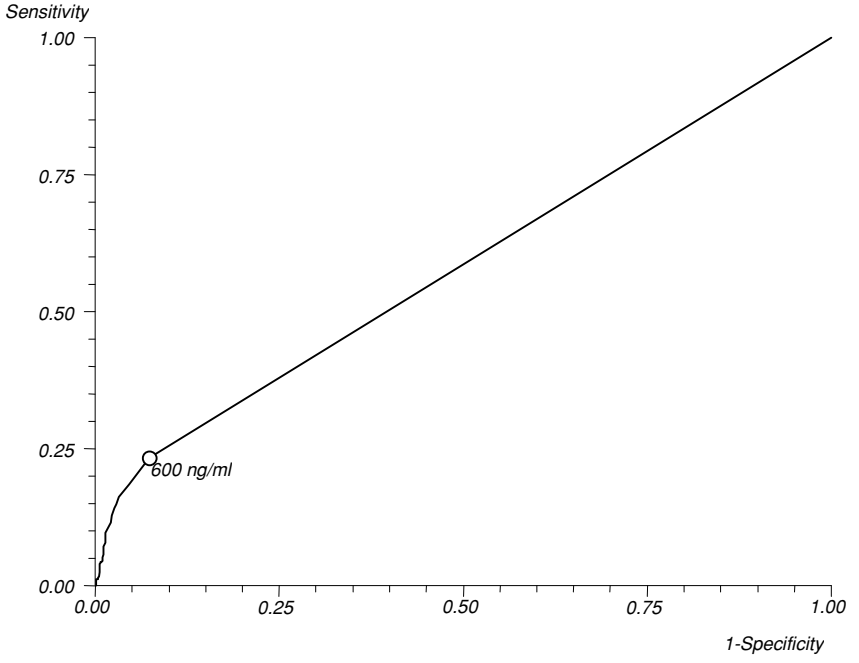


Figure 4. ROC curve for AFP respect to median survival.

Table 7. Immunophenotipic Parameters According to AFP Levels

Mib 1	0	28 (42%)
	1	26 (40%)
	2	12 (18%)
Bcl 2	Low expression	59 (89%)
	High expression	7 (11%)
CD44	0	26 (40%)
	1	14 (21%)
	2	10 (15%)
	3	16 (24%)
P53	Low expression	44 (66%)
	High expression	22 (34%)

in the subgroup of patients undergoing surgery, the prognostic role of AFP was not confirmed. In this series, however, only nine patients with AFP levels exceeding 400 ng/mL underwent resection and this may stand for a bias due to the small size of this specific subgroup.

From a statistical point of view, the significant association between AFP levels and survival was very appealing. However, when we tested our results with the ROC curve, we obtained much less exciting results. On one hand, the specificity of the cutoff chosen (600 ng/mL, therefore higher than the one usually adopted in this kind of studies and even included in the CLIP staging system (18)) was very high (93%); on the other hand, the sensitivity was dramatically low (23%), with an AUC of 0.59, far therefore from the 0.7 value that is considered highly useful. This means that we are quite sure that patients having AFP levels above 600 ng/mL will not have a long survival, but we cannot draw any conclusion on patients with AFP levels lower than that cutoff.

However, also tumor size, that is, the most important parameter in every staging system for HCC and give also several indication for treatment, presents an AUC of 0.61 only with a sensitivity of 48% and a specificity of 69% for the best cutoff, that was 3.9 cm, thus confirming the difficulty in predicting survival with any single mean in the individual patient.

CONCLUSION

AFP confirms also in this large survey its poor diagnostic role with clearly diagnostic level (>400 ng/mL) only in 18% of patients and moderately elevated in 36%. On the other hand, median survival of patients with HCC is related with the levels of the marker at diagnosis, with poorer survival in patients with higher AFP, overall, but with no clear prognostic impact in the individual patient. The poorer median survival of patients with higher level of the marker can be explained by the fact that high AFP levels are related with worst characteristics of tumor such as larger diameter of main lesion, TNM, worse Okuda an Child-Pugh stage, presence of extra hepatic metastases or portal vein thrombosis, association with abdominal pain, or weight loss and possibly by an interaction of the protein with tumor apoptosis.

The biological parameters considered in a subgroup of 66 patients indicate indeed a relationship between high levels of AFP and downregulation of BCL2, thus suggesting a potential biologic role of AFP in regulating apoptosis.

STUDY HIGHLIGHTS

What Is Current Knowledge

- It is unclear if alphafetoprotein provides adequate prognostic information in hepatocellular carcinoma. Coflicting recommendations of the clinical utility of alphafetoprotein have been proposed over the past 3-4 years.

What Is New Here

- Assessment of serum alpphafetoprotein values in a large number of patients with hepatocellular cacrcinoma that were included in this study suggested that alphafetoprotein is not a sensitive marker to detect the presence of hepatocellular carcinoma.
- Prognostic value of alphafetoprotein is limited but correlated with the over survival in untreated patients or those treated with liver transplnantation or locoregional therapies.

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