SHORT COMMUNICATION

Correlation between preoperative serum alpha-fetoprotein levels and survival with respect to the surgical treatment of hepatocellular carcinoma at a tertiary care hospital in Veracruz, Mexico

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KEYWORDS
Hepatocellular carcinoma; Liver resection; Alpha-fetoprotein; Survival

Abstract
Introduction: Preoperative serum alpha-fetoprotein levels can have predictive value for hepatocellular carcinoma survival.
Aim: Our aim was to analyze the correlation between preoperative serum alpha-fetoprotein levels and survival, following the surgical treatment of hepatocellular carcinoma.
Methods: Nineteen patients were prospectively followed (07/2005-01/2016). An ROC curve was created to determine the sensitivity and specificity of alpha-fetoprotein in relation to survival (Kaplan-Meier).
Results: Of the 19 patients evaluated, 57.9% were men. The mean patient age was 68.1 ± 8.5 years and survival at 1, 3, and 5 years was 89.4, 55.9, and 55.9%. The alpha-fetoprotein cut-off point was 15.1 ng/ml (sensitivity 100%, specificity 99.23%). Preoperative alpha-fetoprotein levels below 15.1, 200, 400, and 463 ng/ml correlated with better 1 and 5-year survival rates than levels above 15.1, 200, 400, and 463 ng/ml (P<.05).

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Introducción

Hepatocellular carcinoma (HCC) representa 4% de los cánceres diagnosticados de forma mundial, y es el tercer cáncer más común en el mundo.1 En México, su incidencia ha aumentado en las últimas décadas.2

El alfa-fetoproteína (AFP) es el marcador más importante para el diagnóstico del HCC. Algunos expertos consideran los niveles de AFP > 200 ng/ml como diagnóstico de HCC, mientras que otros consideran los niveles de AFP > 400 ng/ml.3 Elevados niveles de AFP se han asociado con la presencia de lesiones bilobulares y lesiones del vaso portal.4,5 Además, los niveles de AFP han sido utilizados para determinar el valor predictivo de la sobrevida y la recurrencia del HCC.6-8 Sin embargo, no hay consenso sobre el uso de los niveles preoperatorios de AFP para predecir la sobrevida y la recurrencia después de la resección del HCC.

La sobrevida a cinco años después de la resección es de 50-80%.4 En México, la información sobre los niveles preoperatorios de AFP y la sobrevida en pacientes con HCC después de la resección es insuficiente.2,7-10 Nuestra meta fue analizar la correlación entre los niveles preoperatorios de AFP y la sobrevida a cinco años después de la resección del HCC.

Métodos

Un grupo de pacientes con HCC en nuestro hospital que fueron sometidos a resección como tratamiento quirúrgico fueron de forma prospectiva dentro del período de julio de 2005 a enero de 2016, después de obtener la autorización de los expertos locales y el comité de investigación. Los pacientes que fueron excluidos fueron los que recibieron otros tratamientos quirúrgicos (ablation, chemoembolization, transplantation, chemotherapy, and no treatment). Edad, sexo, índice de masa corporal, cirrosis, hepatitis viral, Child-Pugh classification,10 y el model for end-stage liver disease (MELD) score fueron registrados.10 El número de lesiones, tamaño y ubicación, y los niveles preoperatorios de AFP fueron determinados. Los pacientes fueron clasificados de acuerdo con la Organización Mundial de la Salud y el Barcelona Clinic Liver Cancer (BCLC) staging systems.10

Intensive care unit stay, hospital stay, postoperative liver failure, and perioperative mortality fueron documentados. Follow-up was conducted through outpatient consultations. El seguimiento fue definido como la presencia de nuevos hallazgos radiológicos, y la sobrevida fue calculada desde el momento del cierre de la evaluación del paciente hasta su muerte o el final del seguimiento.

Análisis estadístico

Los variables continuas se describieron por medio de media, desviación estándar, y la variable y la variable categórica fueron descritas a través de frecuencia y porcentaje. Una curva de receiver operating characteristic (ROC) se utilizó para determinar el área bajo la curva, punto de corte, y sensibilidad y especificidad de los niveles preoperatorios de AFP para la sobrevida en todos los pacientes, calculado mediante el estimator de Kaplan-Meier. Además, el valor predictivo positivo y el valor predictivo negativo de la curva ROC se determinaron para todos los pacientes. La sobrevida en los pacientes con diferentes niveles preoperatorios de AFP se comparó mediante una prueba de log-rank.

Conclusión

Los niveles preoperatorios de AFP son predictivos de la sobrevida y la recurrencia del HCC. El análisis de los datos en el momento de esta publicación sugiere que los niveles preoperatorios de AFP pueden ser útiles para determinar la sobrevida y la recurrencia después de la resección del HCC.
point, 200 ng/ml, and 400 ng/ml were compared (log-rank, Mantel-Cox). Cox regression was carried out with the different AFP levels to determine the survival risk in those patients. Statistical significance was set at a p < 0.05.

Results

Fifty-two patients were diagnosed with HCC during the study period. Twelve of those patients received no treatment, 14 underwent radiofrequency ablation, 2 had transarterial chemoembolization, and 5 received chemotherapy (sorafenib), all of whom were excluded from the analysis. The study cohort was made up of the remaining 19 patients that underwent resection and 57.9% of them were men (n = 11). The mean age of the study patients was 68.1 ± 8.5 years (range: 44-81) and the mean body mass index was 26.4 ± 3.6 kg/m² (range: 18.5 - 33.3). A total of 26.3% (n = 5) of the patients presented with cirrhosis (Child-Pugh A, etiology: 2 patients with non-alcoholic steatohepatitis, 1 with alcoholic steatohepatitis, and one patient with hepatitis C and alcoholic steatohepatitis). Five patients (26.3%) had hepatitis C virus (4 without cirrhosis). The etiology of liver damage without cirrhosis in the remaining patients was determined in 8 of them (4 with nonalcoholic steatohepatitis and 4 with alcoholic steatohepatitis). The mean AFP level was 463.3 ± 1,057 ng/ml (range: 1.7-4002.4).

The mean lesion size was 6.6 ± 2.4 cm (range: 2-10). Eighteen patients (94.7%) had a single tumor and 63.7% of the lesions were on the right side (n = 12). A total of 52.6% (n = 10) of the patients were classified as Okuda stage I and the mean MELD score was 7.6 ± 2.3 (range: 1-11). All the patients were classified as BCLC stage A.

Eleven patients (57.9%) required treatment in the intensive care unit (1.6 ± 1.9 days, range: 0-7). Mean hospital stay was 8.8 ± 4.9 days (range: 5-21). Three patients (15.7%) had transitory postoperative liver failure. One patient died due to postoperative liver failure and another from a cerebrovascular event. Four patients presented with recurrence (mean 6.8 ± 14.5 months, range: 11-50), resulting in the death of 2 of them, and one patient died from a cardiovascular event (25 months). The estimated overall survival was 55.1 ± 10 months (range: 35.3-74.8) and the actuarial overall survival at one year (13 patients), 3 years (6 patients), and 5 years (6 patients) was 89.4, 55.9, and 55.9%, respectively.

The ROC curve established an area under the curve of 0.987 (95% CI: 0.947-1.0) (p = 0.001), with sensitivity of 100% and specificity of 99.2% for a cutoff point of 15.1 ng/ml, a positive predictive value of 100%, and a negative predictive value of 85.7%. Patients with preoperative AFP levels < 15.1 ng/ml (n = 12) had better survival at one, 3, and 5 years (100%) (mean and median survival: 29 and 15.5 months, respectively) than those with AFP levels > 15.1 ng/ml (n = 7) (71.4, 14.2, and 14.2%; mean and median survival: 23.2 and 14 months, respectively) (p = 0.001, log-rank) (fig. 1A). The patients with preoperative AFP levels < 200 ng/ml (n = 14) (mean and median survival: 32.9 and 205 months, respectively) had a better survival at one, 3, and 5 years (100%)

![Figure 1](image-url)  
**Figure 1**  A) Survival in relation to preoperative AFP of 15.1 ng/ml (p = 0.001). B) Survival in relation to preoperative AFP of 200 ng/ml (p = 0.0001). C) Survival in relation to preoperative AFP of 400 ng/ml (p = 0.0001). D) Survival in relation to preoperative AFP of 463 ng/ml (p = 0.004).

AFP: Alpha-fetoprotein.
and 85.7% at 3 and 5 years) than those with AFP levels > 200 ng/ml (n = 5) (mean and median survival: 10.2 and 14 months, respectively) (60 and 0%, respectively) (p = 0.0001, log-rank) (fig. 1B). Likewise, the patients with preoperative AFP levels < 400 ml (n = 14) (mean and median survival: 32.9 and 205 months, respectively) and with levels of < 463 ng/ml (n = 16) (mean and median survival: 29.7 and 15.5 months, respectively) had better survival at 1, 3, and 5 years (p = 0.0001 and p = 0.004, respectively, through log-rank) (fig. 1C and 1D), compared with the patients with preoperative AFP levels > 400 ng/ml (mean and median survival: 10.2 and 14 months, respectively) and with levels > 463 ng/ml (mean and median survival: 12 and 14 months, respectively). The Cox regression produced no significant differences between the different AFP levels (AFP > 15.16 ng/ml [p = 0.933], AFP > 200 ng/ml [p = 0.938], AFP > 400 ng/ml [p = 0.938], and AFP > 463 ng/ml [p = 0.584]).

Discussion

Our results confirmed the relation of preoperative serum AFP levels to survival in patients that underwent liver resection as HCC treatment. The levels of AFP <15.1 ng/ml and other previously established ones had a statistically significant rate of survival above 5 years. Different studies suggest the relation of an elevated preoperative serum AFP level to the prediction of recurrence, survival, and outcome in HCC.4-6 Tangkijvyanich et al.5 concluded that AFP was useful in the diagnosis and prognosis of patients divided into groups of AFP < 20 ng/ml (normal), markedly elevated (20-399 ng/ml), and very elevated (> 400 ng/ml), with greater survival in the first 2 groups. Likewise, Wen-Jun et al.6 observed that those patients with serum AFP levels < 20 ng/ml had a lower recurrence rate at 2 years and an 18 to 24-month greater survival than the others. Li et al.6 corroborated the fact that liver resection for HCC had a better outcome if the AFP levels were low. Our results offer a cutoff point below 20 ng/ml, with sensitivity and specificity above 90%, and statistically significant differences in survival. The same occurred when the values were > 200 and 400 ng/ml, with no AFP value having greater statistical significance, indicating that the simple elevation of AFP above normal values suggests a worse outcome in those patients.

The relation of the preoperative value of AFP to outcome in patients with HCC has not been studied in Mexico. In 1997, Mondragón Sánchez et al.3 suggested that AFP levels had low sensitivity for diagnosing HCC. Ladrón-de-Guevara et al.7 described mean levels of AFP of 516 ng/ml in patients with HCC, without exploring its influence on outcome. Meza-Junco et al.10 found that 25.2% of patients had an AFP level > 40 ng/ml at diagnosis. Our group previously reported that patients that underwent liver resection had lower AFP levels than other patients, which led to the development of the present study.

Conclusions

Patients with preoperative AFP levels > 15 ng/ml that underwent liver resection as HCC treatment had a lower 5-year survival rate than the patients with AFP levels < 15 ng/ml. Those findings must be corroborated in other case series with different population characteristics.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Financial disclosure

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Conflict of interest

The authors declare that there is no conflict of interest.

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