Baseline characteristics associated with survival in patients with hepatocellular carcinoma

Seymur Aslanov, Nalan Gulsen Unal, Ali Senkaya, Ferit Celik, Abdullah Murat Buyruk, Alper Uysal, Murat Akyildiz, Ilker Turan, Fulya Gunar, Galip Erosh, Abdullah Zeki Karasu, Ahmet Omer Ozutemiz, Ulus Salih Akarca

Division of Gastroenterology, Department of Internal Medicine, University of Ege School of Medicine, Izmir, Turkey; Division of Gastroenterology, Department of Internal Medicine, University of Koc School of Medicine, Istanbul, Turkey

Abstract

Background and Aim: Hepatocellular carcinoma (HCC) is one of the most common and most lethal cancers worldwide. The objective of this study was to investigate the relationship between basal parameters and survival characteristics in patients with HCC.

Materials and Methods: The records of 1,447 HCC patients of a tertiary center during the period 2000-2017 were screened retrospectively. The demographic details; basal clinical, laboratory, and radiological characteristics; treatments; and survival time were recorded and prognostic scores were calculated.

Results: A total of 788 patients with HCC (male/female: 623/165; mean age: 60.5±10.9 years) were included in the study. The median length of survival was 26.3 months (95% confidence interval [CI], 22.3-30.4 months). The 5-year survival rate was 28.1%. The number and diameter of the tumors; platelet count; platelet-to-lymphocyte ratio; level of aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transpeptidase; portal and hepatic vein involvement; and an alpha-fetoprotein level of <9.6 ng/mL were found to be independently related to survival.

Conclusion: The positive predictive value of the prognostic index derived from independent survival-related parameters for 5- and 10-year survival or overall survival was approximately 86%. Integration of this prognostic index to the criteria used in making treatment decisions for patients with HCC should be considered.

Keywords: Alpha-fetoproteins; hepatocellular carcinoma; survival rate.

Introduction

Hepatocellular carcinoma (HCC) represents 85% to 90% of primary liver cancers,[1] HCC is the fifth most common cancer worldwide and third among cancer-related causes of death. Worldwide, 250,000 to 1 million people die from HCC annually. The etiological distribution of HCC varies according to geographical region.[2] In the Far East, the most common cause of HCC is hepatitis B virus (HBV) infection, and >90% of cases develop with a background of cirrhosis, whereas in Western countries, alcohol is a common cause and a high percentage of HCC cases are non-cirrhotic. The growing incidence of fatty liver disease worldwide is associated with an anticipated increase in HCC.[3] Various scoring systems have been developed based on the basal characteristics of the tumors and the liver. However, there is as yet no ideal staging system that meets all needs.

Although there are publications regarding HCC etiology and characteristics in Turkey,[4-7] there is only 1 known study that includes follow-up and survival analysis of a limited number of patients.[8] This study was designed to investigate the relationship between survival and the basal clinical features, laboratory findings, and tumor characteristics of patients with HCC.

Materials and Methods

This study was approved by the Ege University Clinical Research Ethics Committee on September 1, 2018 (no: 18-I/27).

Records of patients with HCC treated during the period 2000-2017 in the hepatology database of the gastroenterology department and Hepato-Pancreato-Biliary Council files were retrospectively screened. Patients <18 years of age, those who had insufficient basal or follow-up data, and those without a definite diagnosis of HCC were excluded. Patients with only minor data missing were included in the binary analysis. The patient demographic data and details of etiology, comorbid illnesses, presence of cirrhosis, decompensation characteristics of patients with cirrhosis, hemogram and biochemical parameters, diameter and number of tumors at diagnosis, radiological and histopathological features (if available), portal venous invasion, hepatic venous invasion, presence of distant metastasis, treatments administered, and survival information were recorded from the electronic files. Based on these data, the Child-Pugh (CP) score, Model For End-stage Liver Disease (MELD) score, Barcelona Clinic Liver Cancer (BCLC) stage, Cancer of the Liver Italian Program (CLIP) score, Okuda stage, and albumin-bilirubin (ALBI) value were calculated. The diagnosis of cirrhosis was based on clinical, radiological, and laboratory findings, as well as the histopathological data available for a few patients. The diagnosis of fatty liver was based on ultrasonographic findings. According to international guidelines, the diagnosis of non-alcoholic steatohepatitis...
(NASH) was based only on liver biopsy findings. Diffuse HCC was defined as a tumor >10 cm in diameter.

For the survival analysis, patient identity numbers were used to search the Death Notification System of the National Ministry of Health (https://obs.saglik.gov.tr) to ascertain which of the study patients had died and the date of death was recorded.

**Statistical Analysis**

The data were analyzed using IBM SPSS Statistics for Windows Version 22.0 (IBM Corp., Armonk, NY, USA) and MedCalc Statistical Software version 19.2 (MedCalc Software bv, Ostend, Belgium). Intergroup differences of categorical data were investigated using a chi-square test. All of the continuous variables were dichotomized according to the cutoff values obtained in receiver operating characteristic (ROC) analysis based on overall survival. These were included in Kaplan-Meier analysis, and the relationship of these parameters to survival time was examined using a log-rank test. Each measurable parameter that demonstrated a relationship to survival time was included in regression analysis using both the raw values and a dichotomized form. Among the dichotomized variables, only alpha-fetoprotein (AFP) was found to be more significant than the raw value for the prediction of survival time and was therefore included in the multiple regression analysis in this form. All of the other measurable parameters were included in the multiple regression analysis in the raw form. The staging system results, MELD score, and CP score were excluded in the multivariate analysis because they consist of basal parameters. A value of p<0.05 was accepted as statistically significant.

**Results**

The analysis was performed using the data of 788 of 1447 patients with HCC. A total of 659 patients were excluded: 47 patients aged <18 years, 352 with insufficient basal data, 229 with insufficient follow-up data, and 31 with an indefinite diagnosis of HCC (Fig. 1).

The distribution of etiologies as well as demographic and clinical data of the patients at the time of diagnosis are shown in Table 1. Of 588 (74.6%) patients with cirrhosis, 312 (53%) had signs of decompensation. Most commonly, this was ascites, which was observed in 284 (36%) patients. In all, 172 (34.1%) had diabetes and 46 (8.7%) patients had a fatty liver.

### Table 1. Clinical features of patients at HCC diagnosis

| Category                                  | n    | %    |
|-------------------------------------------|------|------|
| Gender (male)                             | 623  | 79.1 |
| Age at diagnosis (years)                  |      |      |
| <18 years                                 | 47   | 6.0  |
| 18-65 years                               | 464  | 60.3 |
| ≥66 years                                 | 277  | 33.7 |
| Diagnosis in follow-up period             | 458  | 60.3 |
| Diabetes mellitus                         | 172  | 34.1 |
| Fatty liver                               | 46   | 8.7  |
| Liver biopsy                              | 99   | 12.6 |
| Cirrhosis                                 | 588  | 74.6 |
| Decompensated cirrhosis findings         |      |      |
| Ascites                                   | 284  | 36.0 |
| Hepatic encephalopathy                    | 57   | 7.2  |
| Bleeding esophageal varices               | 67   | 8.5  |
| Child-Pugh classification                  |      |      |
| A                                         | 273  | 46.4 |
| B                                         | 192  | 32.7 |
| C                                         | 108  | 18.4 |
| Portal vein involvement                   | 164  | 20.8 |
| Hepatic vein involvement                  | 33   | 4.2  |
| Lymph node metastasis                     | 9    | 1.1  |
| Distant metastasis                        | 34   | 4.3  |
| Number of tumors                          |      |      |
| 1                                         | 464  | 60.3 |
| 2-3                                       | 145  | 18.8 |
| 4-5                                       | 17   | 2.2  |
| >5 or infiltrated                         | 144  | 18.7 |
| Tumor size                                |      |      |
| <3 cm                                     | 157  | 21.0 |
| 3-5 cm                                    | 140  | 18.7 |
| 5-10 cm                                   | 188  | 25.1 |
| ≥10 cm or diffuse                         | 263  | 35.2 |
| Etiological distribution                  |      |      |
| Hepatitis B                               | 404  | 51.3 |
| Hepatitis C                               | 148  | 18.8 |
| Alcohol                                   | 37   | 4.7  |
| Hepatitis delta                            | 23   | 2.9  |
| Cryptogenic cirrhosis                      | 49   | 6.2  |
| Hepatitis B+alcohol                        | 18   | 2.3  |
| Hepatitis B+hepatitis C                    | 14   | 1.8  |
| NASH                                       | 9    | 1.1  |
| Other                                      | 17   | 2.2  |
| No data                                    | 69   | 8.7  |

a: Calculated using 760 patients with available data; b: Calculated using 505 patients with available data; c: Calculated using 526 patients with available data; d: Calculated using 573 cirrhotic patients with available data; e: Calculated using 770 patients with available data; f: Calculated using 748 patients with available data; g: Other: HCV+alcohol (n=6), Budd-Chiari syndrome (n=2), HBV+autoimmune hepatitis (n=1), HCV+autoimmune hepatitis (n=1), Wilson disease (n=1), primary biliary cholangitis (n=2), autoimmune hepatitis (n=2), Hepatitis B+C+delta (n=1), primary biliary cholangitis +autoimmune hepatitis (n=1), HBV. Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; NASH: Non-alcoholic steatohepatitis.
Table 2. Laboratory features of patients at HCC diagnosis

| Parameter                  | Median | 95% CI of median |
|----------------------------|--------|------------------|
| Neutrophils (x/mm³)        | 3490   | 3200-3614        |
| Lymphocytes (x/mm³)        | 1310   | 1270-1400        |
| Platelets (x/mm³)          | 120000 | 114000-130000    |
| NLR                       | 2.54   | 2.38-2.69        |
| PLR                       | 93.37  | 89.9-100         |
| AST (U/L)                 | 58     | 53-62            |
| ALT (U/L)                 | 41     | 37-44            |
| ALP (U/L)                 | 173    | 157-183          |
| GGT (U/L)                 | 76     | 67-85            |
| Total protein (g/dL)       | 7.3    | 7.3-7.4          |
| Albumin (g/dL)             | 3.50   | 3.5-3.6          |
| Urea (mg/dL)               | 34     | 33-36            |
| Creatinine (mg/dL)         | 1.0    | 1-1              |
| Total bilirubin (mg/dL)    | 1.25   | 1.13-1.33        |
| INR                       | 1.2    | 1.2-1.2          |
| Total cholesterol (mg/dL)  | 154    | 148-158          |
| Triglyceride (mg/dL)       | 87     | 83-91            |
| Na (mEq/L)                | 139    | 139-140          |
| AFP (µg/L)                | 23     | 18-32            |
| LogAFP                    | 1.36   | 1.25-1.5         |
| MELD                      | 10.00  | 10-11            |

AFP: Alpha-fetoprotein; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transpeptidase; HCC: Hepatocellular carcinoma; INR: International normalized ratio; MELD: Model for End-stage Liver Disease; Na: Sodium; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio.

Table 2 shows the laboratory values measured at diagnosis. Although the values are generally consistent with the expected values in cases of cirrhosis, the median parameter values related to liver function, such as albumin, creatinine, total bilirubin, and the international normalized ratio remained within the normal range.

Table 3 provides details of the tumor stage recorded at diagnosis. The BCLC classification data indicated that 404 (51.3%) patients were in stage B, C, or D, signifying that the HCC of approximately half of the study patients was beyond standard curative treatment limits. Of the 700 patients with treatment data, 175 (25%) underwent curative treatment.

Survival Time and Associated Factors

The median length of survival of all of the patients was 26.3 months (95% confidence interval [CI]: 22.3-30.4) (Fig. 2). The median 5-year survival rate was 28.1±0.21%. The survival time of patients diagnosed with HCC during follow-up was longer than that of those who were referred with HCC (median: 35.8 vs. 13.6 months; p<0.0001). The median tumor diameter was 4.7 cm (95% CI: 4.3-5.1) in the former group and 7.9 cm (95% CI: 7.2-8.5) (p<0.0001) in the latter group. The number of tumors was 2.5 (95% CI: 2.2-2.8) and 3.8 (95% CI: 3.4-4.3) (p<0.0001), respectively.

The basal parameters related to survival time are shown in Table 4a. Tumor characteristics and poor prognostic variables were strongly related to survival.

The etiology also had an effect on survival time. Among the 4 most common causes of HCC, the survival time of those with alcohol-related HCC was significantly less than that of the other leading etiologies (Table 5a, b). The length of survival of patients with hepatitis delta-related HCC was longer than that of HBV- or hepatitis C (HCV)-related HCC patients.

The number of tumors and tumor size was closely related to survival time. No significant change in lifespan was observed in cases of ≤3 tumors; the median survival time was 58.0±4.2 months in patients with 1 tumor and 68.4±7.8 months in those with 2-3 tumors. However, when there were >3 tumors, the survival time was significantly reduced. A greater number of tumors is associated with a poor prognosis; however, it is perhaps notable that other poor prognostic indicators were present in patients with more tumors (Table 6). The relationship between the total tumor diameter and survival time is shown in Figure 3. Because the overall survival time of patients with tumor diameters 3-10 cm was similar, tumor size was categorized as <3 cm, 3-10 cm, and ≥10 cm.
Features and survival in hepatocellular carcinoma

Relationship Between Staging Systems and Survival Time

In all staging systems, as the stage progresses, the survival time is dramatically shortened. Staging scores were observed to be associated with survival (Table 3).

The CLIP score was found to be the best predictive score for survival in multivariate analysis (p<0.0001) and had a linear relationship to survival. Stages B and C were the most distinctive in the BCLC staging system based on survival time, but the difference was not statistically significant.

Multiple Regression Analysis

The basal parameters that demonstrated an independent relationship to survival time are presented in Table 4b. A prognostic index using these 10 parameters was calculated by multiplying the B values by the values of corresponding parameters, and summing the results. When the calculated prognostic index was included in ROC analysis with a cutoff of >1.1628, the sensitivity and specificity in predicting overall survival was 66.1% and 78.6%, respectively (area under the curve [AUC]: 0.768). The sensitivity, specificity, positive predictive value (PPV), and AUC values of the same cutoff value to predict a 5- and 10-year cumulative survival time were 66.4%, 78.8%, 82.9%, and 0.772, and 68.5%, 76.9%, 86.2%, and 0.777, respectively. The PPV of the prognostic index was high, that is, it demonstrated a high level of accuracy. The value of this index to predict survival was superior to other known prognostic indices.

Discussion

HCC was associated with HBV in more than half of the patients in this study. HCV infection is the second most common risk factor for HCC. This finding is more similar to those observed in Asian countries, rather than Western countries.[9] Although the overall prevalence of HBV is gradually decreasing,[10] many are diagnosed at an advanced stage of liver disease since >80% of patients are unaware of the disease.[11] Among the most prevalent etiologies, alcohol-related HCC patients had the lowest survival time, which may be due to more advanced liver disease and late diagnosis.[12] Hepatitis delta-related HCC patients had the longest survival, which was associated with the higher transplantation rate in these patients.

Cirrhosis was observed in 74.6% of the study patients. Since the diagnosis of cirrhosis was based on clinical and laboratory data, the actual prevalence might have been higher. Given that 53% of the cirrhosis cases were described as decompensated and that more than half of the patients had a BCLC classification beyond stage A, it appears that the disease is often recognized at an advanced stage. Only 25% of the patients were eligible for curative treatment. Clearly, greater public awareness of hepatitis is needed.

The number and size of tumors were the primary prognostic parameters in our study, as in previous research.[13,14] The Milan criteria and the BCLC specify ≤3 tumors for the application of curative treatment.[15] Survival of our study patients declined sharply in cases of >3 tumors. ROC analysis indicated that the best categorization of tumor size was <3 cm, 3-10 cm, and >10 cm. In this case, the Milan criteria cutoff of 5 cm does not seem to be a wholly appropriate threshold value. It may be that a larger size could be acceptable in patients with good prognostic criteria.

The prognostic value of the different scoring systems were also evaluated. The CLIP scoring system showed the best and most linear relationship to lifespan. The BCLC scoring system was created with the primary aim of directing treatment and it is not technically a prognostic index.
tool. The CLIP score is more comprehensive, as it includes the Child-Pugh grade, AFP value, and tumor size as numerical values.

Among the 10 independent parameters we used in multivariate analysis, tumor size and number, AFP level, and vascular invasion are well known prognostic parameters. However, platelet count, platelet-to-lymphocyte ratio (PLR), and the levels of gamma-glutamyl transferase (GGT), aspartate transaminase (AST), and alanine transaminase (ALT) have not been yet been used in any score. Transaminase elevation increases HCC risk,[16-18] but there are few studies that have examined its relationship to HCC prognosis.[19,20]

The greater damage to liver cells, the greater the enzyme elevation. More cell turnover and inflammation occurs, which increases the risk of cancer[16-18] and recurrence.[20] Some research has indicated that an inflammatory environment appears to be related to HCC prognosis.[21,22] It may be that the instability of transaminase levels prevented the use of these parameters in prognostic scores.

The negative relationship between platelet count and survival is probably related to the acute phase reactant properties of platelets in aggressive and spreading cancers. In recent years, the neutrophil-to-lymphocyte ratio and the PLR have been associated with prognosis in many cancers, and it has been suggested that these ratios can be used as a

**Table 4. Parameter relationship to survival time**

**A. Univariate analysis**

| Parameter                          | B     | SE    | Wald  | df  | Sig.   | Exp (B) | 95.0% CI for Exp (B) |
|------------------------------------|-------|-------|-------|-----|--------|---------|----------------------|
| Number of tumors                   | 0.080 | 0.013 | 38.032| 1   | <0.0001| 1.083   | 1.056 - 1.111        |
| Tumor diameter                     | 0.102 | 0.009 | 130.999| 1  | <0.0001| 1.107   | 1.088 - 1.127        |
| Total tumor diameter               | 0.097 | 0.010 | 96.001| 1  | <0.0001| 1.102   | 1.081 - 1.124        |
| Identification during follow-up    | 0.582 | 0.099 | 34.576| 1  | <0.0001| 1.790   | 1.474 - 2.173        |
| Portal vein involvement            | -0.708| 0.112 | 40.069| 1  | <0.0001| 0.493   | 0.396 - 0.613        |
| Hepatic vein involvement           | -0.599| 0.235 | 6.480 | 1  | 0.011  | 0.549   | 0.346 - 0.871        |
| Distant metastasis                 | -0.791| 0.207 | 14.603| 1  | <0.0001| 0.453   | 0.302 - 0.680        |
| Presence of ascites                | -0.332| 0.100 | 11.036| 1  | 0.001  | 0.717   | 0.590 - 0.873        |
| Neutrophil count                   | 0.110 | 0.027 | 16.739| 1  | <0.0001| 1.116   | 1.059 - 1.176        |
| Platelet count                     | 0.003 | 0.000 | 45.486| 1  | <0.0001| 1.003   | 1.002 - 1.004        |
| NLR                                | 0.049 | 0.008 | 35.916| 1  | <0.0001| 1.050   | 1.034 - 1.067        |
| PLR                                | 0.003 | 0.001 | 23.428| 1  | <0.0001| 1.003   | 1.002 - 1.004        |
| AST                                | 0.002 | 0.000 | 55.203| 1  | <0.0001| 1.002   | 1.002 - 1.003        |
| ALT                                | 0.001 | 0.000 | 7.220 | 1  | 0.007  | 1.001   | 1.000 - 1.002        |
| ALP                                | 0.002 | 0.000 | 61.481| 1  | <0.0001| 1.001   | 1.001 - 1.002        |
| GGT                                | 0.001 | 0.000 | 36.237| 1  | <0.0001| 1.001   | 1.001 - 1.002        |
| Na                                 | -0.043| 0.013 | 11.483| 1  | 0.001  | 0.950   | 0.924 - 0.982        |
| Albumin                            | -0.206| 0.068 | 9.129 | 1  | 0.003  | 0.812   | 0.712 - 0.930        |
| Urea                               | 0.005 | 0.002 | 5.508 | 1  | 0.019  | 1.005   | 1.001 - 1.009        |
| Total bilirubin                    | 0.042 | 0.011 | 14.079| 1  | <0.0001| 1.043   | 1.020 - 1.066        |
| AFP <9.6 ng/mL                     | -0.652| 0.108 | 36.545| 1  | <0.0001| 0.521   | 0.422 - 0.644        |

**B. Multivariate analysis**

| Covariate                         | b      | SE     | Wald  | P      | Exp (B) | 95% CI for Exp (B) |
|-----------------------------------|--------|--------|-------|--------|---------|-------------------|
| Number of tumors                  | 0.05673| 0.01906| 8.8628| 0.0029| 1.0584  | 1.0196 to 1.0987  |
| Tumor diameter                    | 0.09595| 0.01388| 47.7518|<0.0001| 1.1007  | 1.0712 to 1.1311  |
| Platelet count                    | -0.00192| 0.000954| 4.0548| 0.044 | 0.9981  | 0.9962 to 0.9999  |
| PLR                               | 0.002783| 0.000919| 9.1623| 0.0025| 1.0028  | 1.0010 to 1.0046  |
| AST                               | 0.006726| 0.001103| 37.1713|<0.0001| 1.0067  | 1.0046 to 1.0089  |
| ALT                               | -0.00528| 0.002048| 6.6576| 0.0099| 0.9947  | 0.9907 to 0.9987  |
| GGT                               | 0.001502| 0.000487| 9.5107| 0.002 | 1.0015  | 1.0005 to 1.0025  |
| Portal vein involvement           | 0.6732 | 0.1676 | 16.1299| 0.0001| 1.9604  | 1.4115 to 2.7229  |
| Hepatic vein involvement          | -0.761 | 0.3279 | 5.3867| 0.0203| 0.4672  | 0.2457 to 0.8884  |
| AFP <9.6 ng/mL                    | -0.4873| 0.1403 | 12.0702| 0.0005| 0.6143  | 0.4666 to 0.8086  |

- Backward likelihood ratio analysis. Chi-squared=154.171; p<0.0001. AFP: Alpha-fetoprotein; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CI: Confidence interval; GGT: Gamma-glutamyl transpeptidase; Na: Sodium; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio.
Table 5. Survival comparisons

A. Survival time in cases of hepatitis B, hepatitis C, hepatitis delta, and alcoholic liver diseases (months)

| Etiology  | Mean\(^a\) | Median | 95% CI | 95% CI |
|-----------|------------|--------|--------|--------|
|           | Estimate   | SE     | Lower bound | Upper bound |
|           | Estimate   | SE     | Lower bound | Upper bound |
| HBV       | 57.9       | 4.7    | 48.7       | 67.1       |
| HCV       | 67.4       | 7.5    | 52.7       | 82.1       |
| Alcohol   | 40.4       | 11.3   | 18.2       | 62.5       |
| Delta     | 79.6       | 18.4   | 43.6       | 115.6      |
| Overall   | 59.9       | 3.8    | 52.5       | 67.3       |

B. Survival time comparisons in binary groups (p values)

| Etiology  | HBV          | HCV          | Alcohol      | Delta        |
|-----------|--------------|--------------|--------------|--------------|
|           | Estimate     | SE           | Estimate     | SE           |
|           | 0.106        | 0.002        | 0.029        | 0.158        |
|           | 0.029        | 0.495        | 0.033        |              |
|           | 0.158        | 0.033        |              |              |

\(a\): Estimation is limited to the greatest survival time if it is censored; In general comparison: Chi-squared=10.899; p=0.012. CI: Confidence interval; HCV: Hepatitis C virus; HBV: Hepatitis B virus.

Table 6. Factors associated with the number of tumors at the time of diagnosis

| Variables                        | A (n=461) | B (n=145) | C (n=160) | p       | Post hoc test |
|----------------------------------|-----------|-----------|-----------|---------|---------------|
| Gender (% male)                  | 76.1      | 80        | 86.3      | 0.017   |               |
| Follow-up duration before HCC (median-weeks) | 199.5      | 137       | 34        | 0.008   | A-C           |
| Diagnosis in follow-up period (%) | 64.6      | 67.6      | 41.3      | <0.0001 |               |
| Portal vein involvement (%)      | 17.6      | 18.8      | 35.7      | <0.0001 |               |
| Hepatic vein involvement (%)     | 3.1       | 3.5       | 8.5       | 0.026   |               |
| Ascites (%)                      | 31.4      | 41.7      | 47.1      | 0.001   |               |
| Inactive HBV (%)                 | 59.9      | 43.6      | 31.8      | 0.002   |               |
| Log HBV DNA (IU/mL)              | 2         | 2.87      | 3.63      | 0.002   | A-C           |
| Neutrophils (x/mm\(^3\))        | 3732      | 3451      | 4709      | <0.0001 | A-C,B-C       |
| Platelets (x/mm\(^3\))          | 121000    | 92000     | 175500    | <0.0001 | A-B,A-C,B-C   |
| Neutrophil-lymphocyte ratio     | 3.28      | 3.14      | 5.2       | 0.028   | A-C           |
| Platelet-lymphocyte ratio       | 94.2      | 73.5      | 113.57    | <0.0001 | A-B,B-C       |
| AST (U/L)                        | 45        | 49.5      | 65        | <0.0001 | A-C           |
| ALT (U/L)                        | 32.5      | 33        | 44        | 0.003   | A-C           |
| ALP (U/L)                        | 118       | 107       | 146       | <0.0001 | A-C,B-C       |
| GGT (U/L)                        | 67.5      | 63        | 103       | <0.0001 | A-C,B-C       |
| Albumin (g/dL)                   | 3.8       | 3.7       | 3.5       | <0.0001 | A-C,B-A-B     |
| INR                              | 1.1       | 1.1       | 1.2       | 0.01    | A-B           |
| Total bilirubin (mg/dL)          | 1         | 1.13      | 1.3       | <0.0001 | A-B,A-C       |
| Log AFP (ng/mL)                  | 1.15      | 1.47      | 1.65      | <0.0001 | A-C,B-C       |
| MELD                             | 9         | 10        | 10        | 0.001   | A-B,A-C       |
| Child-Pugh                       | 5         | 5         | 6         | <0.0001 |               |

\(A\): Number of tumors: 1; \(B\): Number of tumors: 2 or 3; \(C\): Number of tumors: >3 or infiltrated or multifocal. Post hoc analysis: Comparison of binary groups pairwise analyzed after Kruskal-Wallis analysis. Letters with hyphens between them indicate groups with a significant difference between them. n: The data of 22 patients was not available; the distribution reflects 766 patients. AFP: Alpha-fetoprotein; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transpeptidase; INR: International normalized ratio; MELD: Model for End-stage Liver Disease; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio.
In this study, both parameters were associated with length of survival, however, the PLR was more prominent in the multiple regression analysis. A good prognosis was associated with an AFP of <9.6 ng/mL. In many prognostic systems, the AFP level is excluded. However, it is gradually becoming better understood that this value is important to prognosis, and it is anticipated that AFP may be included in the BCLC in the future. AFP may play a role in the better correlation of the CLIP score to survival time.

The prognostic index derived from multivariate analysis demonstrated a better association with survival than the BCLC, CLIP, Okuda, or ALBI measures in our population. However, it must of course, be validated in other HCC populations to be generally accepted.

### Study Limitations

As in other retrospective observational studies, difficulty obtaining sufficient data and verification were obstacles. Since this is a single-center study, the results cannot be generalized before validation in other populations.

A major drawback of HCC prognostic studies is that treatment can affect prognosis. To our knowledge, the published studies of HCC survival time have all included post-treatment survival in the overall survival analysis. If the treatment time data are eliminated, it is impossible to predict the actual long-term lifespan of patients, and survival data are often obtained using the outcome of late-stage patients who cannot be cured, which also does not reflect the whole truth. It is more realistic to calculate an expected lifespan by including the outcomes of treatment. It is clear that patients who can undergo curative treatment have a better prognosis.

### Conclusion

The number and diameter of tumors, blood platelet count, PLR, AST, ALT, GGT, portal vein involvement, hepatic vein involvement, and an AFP level of <9.6 ng/mL were independently associated with the length of survival of patients with HCC. The positive predictive value of the prognostic index derived from these parameters for 5- and 10-year survival or overall survival was approximately 86%. We should consider integrating this prognostic index into the criteria we use for the treatment decision of patients with HCC.

### Ethics Committee Approval:
The Ege University Clinical Research Ethics Committee granted approval for this study (date: 01.09.2018, number: 18-1/27).

### Peer-review:
Externally peer-reviewed.

### Author Contributions:
Concept – SA, USA, AZK, FG; Design – SA, NGU, USA, AOO; Supervision – USA, FG, AZK; Fundings – AOO, GE, AZK; Materials – SA, AU, FC, MA; Data Collection and/or Processing – AMB, IT, MA, AS, AU, FC; Analysis and/or Interpretation – AOO, AS, NGU, FC, AU, AMB; Literature Search – AS, IT, MA, AMB, GE; Writing – SA, NGU, USA, FG; Critical Reviews – AOO, USA, FG, GE, IT.

### Conflict of Interest:
The authors have no conflict of interest to declare.

### Financial Disclosure:
The authors declared that this study has received no financial support.

### References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394-424.
2. Sanyal A, Yoon S, Lencioni R. The etiology of hepatocellular carcinoma and consequences for treatment. Oncologist 2010;15(S4):14-22.
3. Paul S, Dhamija E, Kedia S. Non-alcoholic fatty liver disease associated with hepatocellular carcinoma: An increasing concern. Indian J Med Res 2019;149(1):9.
4. Uzunalimoğlu Ö, Yurdaydın C, Çetinkaya H, Sahin T, Colakoğlu S, Tankurt E, et al. Risk Factors for Hepatocellular Carcinoma in Turkey. Dig Dis Sci 2001;46(5):1022-1028.
5. Can A, Dogan E, Bayoglu I, Tatli A, Tatli AM, Besiroğlu M, Kocer M, et al. Multicenter epidemiologic study on hepatocellular carcinoma in Turkey. Asian Pac J Cancer Prev 2014;15(6):2923-2927.
6. Akkiz H, Carr B, Yalçın KK, Guerra V, Kuran S, Altuntas E, et al. Characteristics of hepatocellular carcinoma aggressiveness factors in Turkish patients. Oncology 2017;94(2):116-124.
7. Ekinci O, Baran B, Ormeci A, Soyer OM, Gokturk S, Evirgen S, et al. Current state and clinical outcome in Turkish patients with hepatocellular carcinoma. World J Hepatol 2018;10(1):51-61.
8. Alacacioglu A, Somali I, Simsek I, Astarciclioglu I, Ozkan M, Cameci C, et al. Epidemiology and survival of hepatocellular carcinoma in Turkey: outcome of multicenter study. Jpn J Clin Oncol 2008;38(10):683-688.
9. El-Serag H. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology. 2012;142(6):1264-1273.e1.
10. Girol E, Saban C, Oral O, Cigdem A, Armagan A. Trends in hepatitis B and hepatitis C virus among blood donors over 16 years in Turkey. Eur J Epidemiol. 2006;21(4):299-305.
11. Tozun N, Ozdogan O, Cakaloglu Y, Ildihan R, Karasu Z, Akcar U, et al. Serum prevalence of hepatitis B and C virus infections and risk factors in Turkey: a fieldwork TURHEP study. Clin Microbiol Infect. 2015;21(11):1020-1026.
12. Schütte K, Bornschein J, Kahl S, Seidensticker R, Arend J, Ricke J, et al. Delayed diagnosis of hep c with chronic alcoholic liver disease. Liver Cancer. 2012;1(3-4):257-266.
13. Wu G, Wu J, Wang B, Zhu X, Shi X, Ding Y. Importance of tumor size at diagnosis as a prognostic factor for hepatocellular carcinoma survival: a population-based study. Cancer Manag Res 2018;10:4401-4410.
14. Mazzaferro V, Llovet J, Miceli R, Bhoori S, Schiavo M, Mariani L, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 2009;10(10):35-43.
15. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334(11):693-700.
16. Ishiguro S, Inoue M, Tanaka Y, Mizokami M, Iwashiki M, Tsugane S, et al.; JPHC Study Group. Serum aminotransferase level and the risk of hepatocellular carcinoma: a population-based cohort study in Japan. Eur J Cancer Prev. 2009;18(1):26-32.
17. Suruki R, Hayashi K, Kusumoto K, Uto H, Ido A, Tsoubouchi H, et al. Alanine aminotransferase level as a predictor of hepatitis C virus-associated hepatocellular carcinoma incidence in a community-based population in Japan. Int J Cancer 2006;119(1):192-195.
18. Wen C, Lin J, Yang Y, Tsai MK, Tsao CK, Etzel C, et al. Hepatocellular carcinoma risk prediction model for the general population: the predictive power of transaminases. J Natl Cancer Inst 2012;104(20):1599-1611.
19. Carr IB, Guerra V. A hepatocellular carcinoma aggressiveness index and its relationship to liver enzyme levels. Oncology 2016;90(4):215-220.
20. Tarao K, Takemura S, Taiwai S, Sugimasa Y, Ohkawa S, Akaike M, et al. Relationship between the recurrence of hepatocellular carcinoma (HCC) and serum alanine aminotransferase levels in hepatocetomized patients with hepatitis C virus-associated cirrhosis and HCC. Cancer 1997;79(4):688-694.
sociated advanced hepatocellular carcinoma. Oncol Lett 2017;14(2):2089-2096.

22. Zhao L, Yang D, Ma X, Liu MM, Wu DH, Zhang XP, et al. The Prognostic Value of aspartate aminotransferase to lymphocyte ratio and systemic immune-inflammation index for Overall Survival of Hepatocellular Carcinoma Patients Treated with palliative Treatments. J Cancer 2019;10(10):2299-2311.

23. Hung H, Lee J, Cheng C, Wu TH, Wang YC, Lee CF, et al. Impact of neutrophil to lymphocyte ratio on survival for hepatocellular carcinoma after curative resection. J Hepatobiliary Pancreat Sci 2017;24(10):559-569.

24. Wang Y, Attar B, Fuentes H, Jaiswal P, Tafur AJ. Evaluation of the prognostic value of platelet to lymphocyte ratio in patients with hepatocellular carcinoma. J Gastrointest Oncol 2017;8(6):1065-1071.