Baseline Characteristics Associated with Survival in Patients with Hepatocellular Carcinoma

Seymur Aslanov[1], 0000-0001-7520-6650
Nalan Gülşen Ünal[2], 0000-0001-8870-2450
Ali Şenkaya[3], 0000-0002-5787-3422
Ferit Çelik[3], 0000-0003-4459-7657
Abdullah Murat Buyruk[3], 0000-0002-7233-2042
Alper Uysal[3], 0000-0002-5473-9383
Murat Akyıldız[2], 0000-0002-2080-7528
İlker Turan[3], 0000-0001-8998-1965
Fulya Günşar[3], 0000-0002-6002-4819
Galip Ersöz[3], 0000-0002-2040-7524
Abdullah Zeki Karasu[3], 0000-0002-4974-7944
Ahmet Ömer Ömer[3], 0000-0002-6960-4043
Ulus Salih Akarca[3], 0000-0002-7020-5816

[1]Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, University of Ege, Izmir, Turkey
[2]Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, University of Koç, Istanbul, Turkey
[3]Ege University Medical Faculty, Department of Internal Medicine, Division of Gastroenterology, Izmir, Turkey

Corresponding Author: Seymur ASLANOV M.D.
Mailingaddress: Ege University, Faculty of Medicine, Department of InternalMedicine, Division of Gastroenterology, 35100, Bornova, Izmir, TURKEY
Telephone: +902323904397
Mobile phone: +905070481605

Abstract

Background and Aim: HCC (hepatocellular carcinoma) is one of the most commonly seen and lethal cancers worldwide. We aimed to investigate the relationship between basal parameters, and survival characteristics in patients with HCC.

Materials and Methods: In a tertiary center 1447 patients were screened between 2000 and 2017, retrospectively. The demographics, basal clinical, laboratory, and radiological characteristics, treatments, and survival time were recorded and prognostic scoring systems calculated.

Results: Seven hundred eighty eight patients (M/F: 623/ 165, mean age: 60. 5±10. 9) with HCC were included to the study. The median survival time was 26.3 months (95% CI, 22.3-30.4). The 5-year survival rate was 28.1%. The number and diameter of tumors, platelet count, platelet-to-lymphocyte ratio, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, portal and hepatic vein involvement, AFP being <9.6 ng/ml were found independently related with survival.

Conclusions: The positive predictive value of the prognostic index derived from independent survival-related parameters in predicting 5- and 10-years 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.

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INTRODUCTION

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

In our country, although publications regarding HCC etiology and characteristics are available[4–7], only one study conducted follow-up and survival analyses in a limited number of patients[8].

In this study, we aimed to investigate the relationship between basal clinical features, laboratory findings, and tumor characteristics with survival in patients with HCC.

MATERIALS AND METHOD

Patients with HCC were retrospectively screened from the hepatology database of the gastroenterology department, and hepato-pancreato-biliary council files, between 2000 and 2017. The patients <18 years, who had insufficient basal or follow-up data, those with not definite diagnosis of HCC were excluded. Patients with minor missing data were included in the study for the binary analysis. The study was approved by the local ethics committee (18-1/27 dated 01.09.2018).

The demographic data, etiologies, comorbid illnesses, presence of cirrhosis, decompensation characteristics of patients with cirrhosis, hemogram and biochemical parameters, diameter and number of tumors at diagnosis, radiological and if any, histopathological features, portal venous invasion (PVI), and hepatic venous invasion (HVI), presence of distant metastasis, treatments received, and survival information were recorded from the electronic files. Based on these data, the patients' Child–Pugh (CP) score and model for end-stage liver disease (MELD) scores, Barcelona Clinic Liver Cancer (BCLC) stages, Cancer of the Liver Italian Program (CLIP) scores, Okuda stages, and albumin–bilirubin (ALBI) grades were calculated. The diagnosis of cirrhosis was based on clinical, radiological, and laboratory findings, and on histopathological data in a few patients. The diagnosis of fatty liver diagnosis was based on ultrasonographic findings. According to international guidelines, the diagnosis of non-alcoholic steatohepatitis (NASH) was based only on liver biopsy. Diffuse HCCs were considered to be >10 cm in diameter.

For survival analysis, all patients with an identity number were searched in the Death Notification System of the National Ministry of Health (https://obs.saglik.gov.tr), and the dates of death were recorded. The patients who are alive were recorded as living until the analysis date.

Statistical analysis: The data were analyzed using IBM SPSS Statistics Version 22.0, and MedCalc Statistical Software version 19.2 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020). Intergroup differences of categorical data were investigated using

the chi-squared test. All continuous variables were dichotomized according to the cut-off values obtained in the receiver operating characteristic (ROC) analysis based on overall survival. By including these into the Kaplan–Meier analysis, the relationships of these parameters with survival time were also investigated using log-rank test. Each measurable parameter that shows a relationship with survival time was included into the regression analysis both with its obtained raw values and dichotomized form. Among the dichotomized variables, only alphafetoprotein (AFP) was found to be more significant compared with the raw value in predicting survival time and included in the multiple regression analysis in this form. All other measurable parameters were included in the multiple regression analysis in their raw forms. Staging systems, MELD score, and CP score were excluded in the multivariate analysis because they consisted of basal parameters. In the analysis, $p<0.05$ was accepted as statistically significant.

RESULTS

The analysis included 788 of 1447 patients with HCC. The study excluded 659 patients, including 47 patients aged <18 years, 352 with insufficient basal data, 229 with insufficient follow-up data, and 31 with suspicious diagnosis of HCC (figure 1).

The distribution of etiologies and demographic and clinical data of patients at diagnosis are shown in Table 1. Of 588 (74.6%) patients with cirrhosis, 312 (53%) had signs of decompensation, with ascites as the most common in 284 (36%) patients. In addition, 172 (34.1%) and 46 (8.7%) patients had diabetes and fatty liver, respectively.

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

Table 3 shows the tumor stages at diagnosis. According to BCLC classification, 404 (51.3%) patients were in stages B, C, and D, indicating that approximately half of the patients were outside the curative treatment limits.

With regard to treatment, 175 (25%) of 700 patients with treatment data underwent curative treatment.

Survival Times and Associated Factors

The median survival time of all patients was 26.3 months (95% CI,22.3–30.4) (Figure 2). The 5-year survival rate was 28.1%±0.21%. In patients diagnosed during follow-up, the survival time was longer than those who 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, and 7.9 cm (95% CI, 7.2–8.5) ($p<0.0001$) in the latter groups. 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 with survival time are shown in Table 4-A. Tumor characteristics and poor prognostic variables strongly related to survival.

The difference in survival time was seen in patients with HCC with different etiologies. Based on the four most common causes of HCC, alcohol-related HCC's survival times were significantly shorter comparing to the others (Table 5-A and B). Survivial of delta-related HCC seemed to be longer than those of HBV or HCV-related HCCs.

The number of tumors and tumor size was closely related with survival time. No significant change in lifespan was observed in up to three tumors. In patients with 1 tumor and those with 2–3 tumors, the survival time was 58.0±4.2 and 68.4±7.8 months, respectively; however, when the number of tumors was >3, the survival time was significantly reduced. Certainly, higher number of tumors is associated with poor prognosis; however, other poor prognostic indicators are present in patients with higher number of tumors (Table 6). The relationship between total tumor diameter and survival time is shown in Figure 3. Because the overall survival time of patients with tumor diameters between 3 and 10 cm was similar, tumor size was categorized as <3 cm, 3–10 cm, and ≥10 cm.

Relationship Between Staging Systems and Survival Time

Staging systems were associated with survival of patients with HCC patients (Table 3). In all staging systems, as the stage progresses, the survival time is dramatically shortened.

The CLIP score was found to be the best predictive score for survival with multivariate analysis ($p<0.0001$) and had a linear relationship with survival. The B and C stages were found to be 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 showing independent relationship with survival time are seen in Table 4-B. A prognostic index was calculated by using these 10 parameters, which was derived by multiplying the b values with the values of corresponding parameters, and summation of these numbers. When the calculated prognostic index was included in the ROC analysis, and the cut-off was >1.1628, its sensitivity and specificity in predicting overall survival were 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 cut-off value in predicting 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 is high, that is, a high percentage of predicting deaths. The value of this index to predict the survival was found to be superior comparing to the known prognostic indices.

Discussion

HCC was associated with HBV in more than half of the patients. Hepatitis C virus (HCV) infection is the second most common risk factor for HCC. This feature resembles the characteristics in Asian countries, rather than Western countries[9]. Although hepatitis B prevalence is gradually decreasing[10], because of the unawareness of >80% of patients about their own disease[11], several patients are diagnosed at advanced stages of liver disease. Among the most prevalent etiologies, alcohol-related HCCs have the lowest survival time, which may be due to patients having more advanced liver disease and being diagnosed late[12]. Hepatitis delta-related HCC have the longest survival time, which was associated with the higher transplantation rate in these patients.

Cirrhosis was described in 74.6% of the patients. Since the diagnosis of cirrhosis was based on clinical and laboratory data, the actual prevalance might be higher. Given that 53% of cirrhosis of the liver has been decompensated and more than half of the patients in the BCLC scoring system have passed stage A, it appears that the patients are recognized at an advanced stage. Thus, only 25% of the patients were able to benefit from the chance of the curative treatment. It is obvious that public awareness of hepatitis should be raised.

Tumor number and size were the main prognostic parameters in our study, like most of the others[13,14]. In order to apply a curative treatment, the number of tumors in Milan criteria and in BCLC should be ≤3, which was definitely confirmed in our study[15]. Survival declined sharply over the number of 3. ROC analyses indicated that the best categorization of tumor size was <3cm, 3-10 cm, and >10 cm. In this case, the cut-off of 5 cm according to the Milan criteria does not seem to be a correct treshold value. It must be argued that, in patients with good prognostic criteria, tumor size can be expanded according to the Milan criteria.

The prognostic values of different scoring systems in our population are also evaluated on this occasion. CLIP scoring showed the best and most linear relationship with life span. BCLC scoring was created with the concern of directing the treatment and it is not a real scoring system. However, in the CLIP score, Child Pugh grade, AFP and tumor size are included as numerical values.

Among the 10 independent parameters in multivariate analysis, tumor size and number, AFP level, and vascular invasion are well known prognostic parameters and place in differents prognostic scores. However, platelet count, PLR, AST, ALT, and GGT have not been included in any score. In fact, transaminase elevation mostly increases HCC risk[16–18], but studies showing its relationship with HCC prognosis are relatively fewer[19,20]. The more the liver cells are damaged, the higher the enzymes are elevated, and more cell turnover and inflammation occurs, which increases cancer recurrence risk[20] along with cancer risk[16–18]. Some studies also show that inflammatory environment is related with HCC prognosis[21,22]. Probably, transaminase levels being too unstable may have prevented these parameters to be included in prognostic scores.

The negative relation with platelet count and the survival probably related to acute phase reactant properties of platelets in aggressive and spreading cancers. In recent years, the NLR and PLR were associated with prognosis in many cancers, and it was defended that they can be used as a marker[23,24]. In this study, both parameters were also associated with survival time. However, PLR became more prominent in multiple regression analysis. Good prognosis was associated with AFP<9.6 ng/ml. In many prognostic systems, the AFP level is excluded. However, it is gradually being better understood that it is important in prognosis, and AFP is anticipated to be included in BCLC in the future. AFP may play a role in CLIP score being better correlated with survival time.

The prognostic index derived from multivariate analyse showed better association with survival comparing to BCLC, CLIP, Okuda or ALBI, in our population. However, it is obvious that to be generally accepted, it must be validated in other HCC populations.

Limitations of the study

As the other retrospective observational studies, difficulty in reaching to every data, and verification remain as major obstacles. Since this is a single center study, the results can not be generalized before validation in other populations.

An unresolvable major drawback of HCC prognostic studies is the treatment methods and results of the treated patients affecting prognosis. In all HCC survival time studies, post-treatment survival times are included in the overall survival analysis. If the treatment time is censored, it becomes impossible to predict the actual long-term lifespan of patients, and survival data is often obtained with the outcome of late-stage patients who cannot be cured, which is not reflect the truth. It is more realistic to calculate the life span by including the outcomes of the treatments. Because it is clear that patients who can be performed curative treatment are already patients with good prognosis.

CONCLUSIONS

In conclusion, the number and diameter of tumors, blood platelet count, PLR, AST, ALT, GGT, portal vein involvement, hepatic vein involvement, and AFP <9.6 ng/ml were independently associated with survival of patients with HCC. The positive predictive value of the prognostic index derived from these parameters in predicting 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.

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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, Yurdaydin C, Çetinkaya H, 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, 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, et al. Characteristics of hepatocellular carcinoma aggressiveness factors in Turkish patients. Oncology. 2017;94(2):116-124.

7. Ekinci O, Baran B, Ormeci A, 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, 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. Gurol 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, et al. Seroprevalence 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, et al. Delayed diagnosis of hcc 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, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol. 2009;10(1):35-43.

15. Mazzaferro V, Regalia E, Doci R, 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, et al. 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, 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, 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, Takemiya S, Tamai S, et al. Relationship between the recurrence of hepatocellular carcinoma (HCC) and serum alanine aminotransferase levels in hepatectomized patients with hepatitis C virus-associated cirrhosis and HCC. Cancer. 1997;79(4):688-694.

21. Hong Y, Chen Z, Wei L, et al. Identification of the prognostic value of lymphocyte-to-monocyte ratio in patients with HBV-associated advanced hepatocellular carcinoma. Oncol Lett. 2017;14(2):2089-2096.

22. Zhao L, Yang D, Ma X, 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, 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.

Table 1. Clinical features of patients during HCC diagnosis.

	n	%
Gender (male)	623	79.1
Age of diagnosis (years)	60. 5±10. 9	
Diagnosis in follow-up period	458[a]	60.3
Diabetes mellitus	172[b]	34.1
Fatty liver	46[c]	8.7
Liver biopsy	99	12.6
Cirrhosis	588	74.6
Decompensated cirrhosis findings		
Ascites	284	36.0
Hepatic encephalopathy	57	7.2
Esophageal varices bleeding	67	8.5
Child-Pugh[d]		
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[e]		

1	464	60.3
2-3	145	18.8
4-5	17	2.2
>5 or infiltrated	144	18.7
Tumor size[f]		
<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
Others[g]	17	2.2
No data	69	8.7

a:calculated over 760 patients who have available data; b:calculated over 505 patients who have available data; c: calculated over 526 patients who have available data.
d: calculated over 573 cirrhotic patients who have available data; e: calculated over 770 patients who have available data; f: calculated over 748 patients who have available data.;g: Others: HCV+Alcohol(n=6), Budd Chiari (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);n:number of patient

Table 2. Laboratory features of patients during HCC diagnosis.

	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 (g/L)	23	18-32
LogAFP	1.36	1.25-1.5
MELD	10.00	10-11

NLR: Neutrophil-lymphocyte ratio;PLR: Platelet-lymphocyte ratio; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyltranspeptidase; INR: İnternational normalized ratio; Na: Sodium; AFP: Alpha-fetoprotein; MELD: Model For End-Stage Liver Disease; CI: Confidence Interval

Table 3. Relationship of staging systems with survival time.

Scoring systems	Subgroups	N (%)	ST(month)	5% CI		p
				Lowerlimit	Upper limit	
BCLC	0	89 (11.3)	51.9	19.4	84.5	<0.0001
	A	295 (37.4)	36.7	28.3	45.1	
	B	139 (17.6)	21.5	15.8	27.1	
	C	145 (18.4)	8.5	5.4	11.7	
	D	120 (15.2)	7.8	3.5	30.4	
CLIP[a]	0	159 (24.1)	45.5	35.1	55.8	<0.0001
	1	176 (26.7)	31.6	24.5	38.8	
	2	150 (22.8)	18.5	12.7	24.3	
	3	90 (13.7)	8.3	6.0	10.6	
	4	58 (8.8)	5.1	2.7	7.5	
	5	24 (3.6)	2.5	1.3	3.8	
	6	2 (0.3)	0.9	0.9	1.9	
OKUDA[b]	1	293 (39.3)	36.7	28.9	44.5	<0.0001
	2	383 (51.4)	16.6	11.9	21.3	
	3	69 (9.3)	3.9	1.2	6.7	
ALBI[c]	1	204 (27.2)	36.2	28.9	43.6	0.003
	2	392 (52.2)	22.8	16.6	29.1	
	3	155 (20.6)	8.8	3.2	14.3	

a: 129 patients could not be evaluated ; b: 43 patients could not be evaluated; c: 37 patients could not be evaluated. ST: Survival Time ; CI: Confidence interval ; N: Number of patient; BCLC: Barcelona,CLIP : Cancer of the Liver Italian Program ; ALBI: Albumin-bilirubin

Table 4. The parameters that show relationship with survival time. A: Univariate, B: Multivariate analysis results.

A

	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	1,002	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	0,958	0,934	0,982
Albumin	-0,206	0,068	9,129	1	0,003	0,814	0,712	0,930
Urea	0,005	0,002	5,508	1	0,019	1,005	1,001	1,009
TotalBilirubin	0,042	0,011	14,079	1	<0,0001	1,043	1,020	1,066
AFP being <9.6 ng/ml	-0,652	0,108	36,545	1	<0,0001	0,521	0,422	0,644

B

Covariate	**b**	**SE**	**Wald**	**P**	**Exp(b)**	**95% CI of 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
Portalvein 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 being <9.6 ng/ml	-0.4873	0.1403	12.0702	0.0005	0.6143	0.4666 to 0.8086

-Backward likelihood ratio analysis. Chi square=154.171, p<0.0001
-NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyltranspeptidase; Na: Sodium; AFP: Alpha-fetoprotein; CI: Confidence Interval; SE: Standard Error

Table 5. A: Survival times in Hepatitis B, hepatitis C, delta hepatitis and alcoholic liver diseases (in months), B: survival time comparisons in binary groups (p values).

A

Etiology	**Mean[a]**				**Median**			
	Estimate	Std. Error	95% Confidence Interval		Esti-mate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
HBV	57.9	4.7	48.7	67.1	**27**	3.3	20.5	33.5
HCV	67.4	7.5	52.7	82.1	**42.5**	8.1	26.5	58.4
Alcohol	40.4	11.3	18.2	62.5	**12.5**	5.4	1.9	23.0
Delta	79.6	18.4	43.6	115.6	**68.3**	30.4	8.7	127.9
Overall	59.9	3.8	52.5	67.3	**29.8**	2.6	24.7	34.8

a: Estimation is limited to the largest survival time if it is censored; HBV:Hepatitis B Virus ; HCV: Hepatitis C Virus

In general comparison of all of them Chi-square=10. 899; p=0. 012

B

Etiology	**HBV**	**HCV**	**Alcohol**	**Delta**
HBV		0.106	**0.029**	0.158
HCV	0.106		**0.002**	0.495

Alcohol	**0.029**	**0.002**		**0.033**
Delta	0.158	0.495	**0.033**	

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

Variables	A (n=461)	B (n=145)	C (n=160)	p	PostHoc test
Gender (% male)	76.1	80	86.3	0.017	
Follow-up duration before HCC (median-week)	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/mm3)	3732	3451	4709	<0.0001	A-C,B-C
Platelets (x/mm3)	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,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 analysedafter Kruskal-Wallis analysis. The letters with hyphens between them represent the groups that the difference in between was found significant .n-number of patient(since the data of 22 patients could not be reached, the distribution was shown over 766 patients. HBV: Hepatitis B virus ;AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyltranspeptidase; INR: İnternational normalized ratio; AFP: Alpha-fetoprotein; MELD: Model For End-Stage Liver Disease.

Figure legends

Fig.1. Flow diagram of the study.

Fig.2. Survival time of all patients (median 26.3 months)

Fig.3. Survival time graphics according to tumor sizes. (3-<10 cm was taken as a single group) Log-rank test p<0. 0001