Original Research

CLINICAL AND LABORATORY CHARACTERISTICS AND PROGNOSIS OF PATIENTS WITH HEPATOCELLULAR CARCINOMA

Nguyen Thi Hong Chuyen[1*], Tran Anh Thuy Duong[1], Nguyen Thi Thu Giang[1], Tran Thi Quyen[1], Phung Phuong[1], Dang Cong Thuan[1], Nguyen Van Cau[1], Nguyen Tran Thuc Huan[1], Nguyen Thanh Phuc[1], Le Thanh Huy[1]

DOI: 10.38103/jcmhch.2021.72.9

ABSTRACT

Purpose: *We investigated the influence of baseline characteristics of patients with hepatocellular carcinoma (HCC) on prognosis.*

Methods: *A Retrospective descriptive study on patients with HCC was carry out at the Oncology Department of Hue University of Medicine and Pharmacy Hospital and Hue Central Hospital (HCH), Viet Nam, from Oct 2015 to Dec 2019. Demographic, laboratory, tumor characteristics, and performance status were determined before treatment. Predictors of survival were identified using the Kaplan - Meir test and the Cox model.*

Result: *A total of 261 patients, 87.4% male; median age was 58.4; 80,1% of patients admitted to hospital because of right upper quadrant pain. 45.2% ECOG 0, 51.7% ECOG 1; AFP > 400 ng/mlhas 67.4%. The most robust predictors of survival were tumor size, ECOG, portal vein tumor thrombus, Barcelona Clinic Liver Cancer (BCLC), initial treatment. Overall survival in patients with HCC was 9.0 months. In a multivariate analysis: BCLC and initial treatment modalities were independent predictors of survival.*

Conclusions - Patients with HCC had a poor survival with a median of nine months. Five easily measurable clinical variables were significant predictors of survival in patients with HCC.

Keywords: *Hepatocellular carcinoma; clinical presentation; prognostic model.*

I. INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common tumor in Viet Nam following GLOBOCAN 2020. In Viet Nam, the incidence and mortality of HCC have been the first rank among 26.418 new cases and 25.272 deaths [1]. Furthermore, the incidence rate is almost equal to the death rate indicating that HCC is often detected at a late stage and has a poor prognosis [2,3]. In the 11 most popular cancers, HCC has the lowest overall survival with a five - year survival rate of 18 percent. Most patients are detected at the progression of the advanced stage. This was not suitable for radical treatments. In addition, HCC patients often have chronic liver disease (chronic hepatitis, cirrhosis). This limits the possibility of specific treatment [4,5]. With HCC patients, an accurate prognosis is significant and is the main requirement in treating HCC. Therefore, it is important to understand the

[1]Hue University of Medicine and Pharmacy Hospital

- **Received:** 28/9/2021; **Revised:** 15/10/2021;
- **Accepted:** 18/10/2021
- **Corresponding author:** Nguyen Thi Hong Chuyen
- **Email:** hongchuyen0620@yahoo.com.vn; **Phone:** 0935660610

factors that predict the survival of patients with HCC. In some studies, several key factors that may affect the prognosis of survival with HCC have been identified: diagnosis stage, the overall health of the patient, hepatic function, tumor biomarkers, and efficacy of treatment. However, these factors have recently been much debated [6,7,8]. In Vietnam, these studies are not yet popular. So we conducted a study: "Clinical and laboratory characteristics and prognosis of Hepatocellular Carcinoma". This study aims to investigate clinical features and laboratory findings of HCC and identify independent predictors of survival at the time of diagnosis in a single center.

II. MATERIALS AND METHODS

1. Materials

This retrospective study involved 261 patients diagnosed with HCC undergoing treatment at the Department of Oncology in Hue central hospital and of Hue University of Medicine and Pharmacy Hospital, Vietnam, between October 2015 and December 2019. Within this final cohort of patients, HCC was diagnosed by the guidelines for HCC by The VN Ministry of Health in 2012. The patients agreed to participate in this study and have sufficient medical record documentation.

The diagnostic criteria of HCC are based on diagnosis and treatment guidelines of the Vietnamese Ministry of Health 2012 satisfying 1 of 3 criteria: (1) evidence of pathological diagnosis with HCC, (2) typical image of HCC on contrast - enhanced abdominal computer tomography or magnetic resonance image together with AFP level higher than 400 ng/mL, or (3) typical image of HCC on contrast - enhanced abdominal computer tomography or magnetic resonance image, with an increase in AFP (but less than 400 ng/mL) and evidence of chronic HBV or HCV infection.

A typical image of HCC on contrast-enhanced abdominal computer tomography or magnetic resonance image show enhancement at the arterial phase and wash-out at the portal and delayed phase, or tumor is hypodense on non - contrast-enhanced CT and hyperdense on late arterial phase.

2. Methods

All included cases were first summarized and then analyzed. Our primary endpoint was overall survival (OS). The second aim was to determine some predicted factors.We retrospectively analyzedcharacteristics that may affect the prognosis of patients with HCC including Child - Pugh classification, Barcelona clinic liver cancer (BCLC) stage, tumor size, portal vein tumor thrombus (PVTT), and therapy. The therapies in our center include surgery, radiofrequency ablation (RFA) only, transarterial chemo - embolization (TACE) only, transarterial oily chemo - embolization (TOCE) only, Sorafenib, and symptomatic treatment. Finally, we used the significant variables from univariate analysis in multivariate Cox model analysis to confirm the significant and independent impact of HCC survival time.

In the study, we took the factors which may be related to the prognosis of HCC or controversial in other studies into the analysis. We defined the number of tumor nodules, and the presence of PVTT, according to abdominal ultrasound, abdominal computed tomography, or magnetic resonance imaging findings, or surgical observations. The patients were followed up. We defined survival time as the time elapsed between the diagnosed time and the date of death before ending the study or December 2020.

The Kaplan - Meier method was used to estimate survival, the log - rank test analyses the relevant factors. The Cox proportional hazards model was used for the multivariate analysis of significant survival variables from the Kaplan - Meier method. Statistical significance was determined at $P < 0.05$.

All statistical analyses were performed with SPSS software version 16

III. RESULTS

1. Clinical and laboratory characteristics

Baseline characteristics are summarized in Table 1. Male gender (87.4%) was predominant, and the mean age was 58.4 +/- 11.6 years. There were 87 hepatitis B, C (33,4%), 14 liver cirrhosis (5,4%). For

clinical features, 260 patients (99,6%) had ECOG 0/1/2, a patient ECOG 3 only. The major symptom was right hypochondriac pain, fatigue, and anorexia. Only 9 patients (3,4%) had detected it accidentally. 176 patients (67,4%) increased AFP over 400 ng/ml. Two hundred twenty - two patients were positive for HBsAg or anti HCV or both (85,1%). Child - pugh A B patients accounted for 253 (96,9%). Data showed that 117 patients (44,8%) had single tumor nodules and 201 whose tumors (77%) were larger than 5cm in size. Over half of patients (50,2%) presented portal vein thrombus. In total, our HCC patients were predominant BCLC, with 168 patients (64,4%), 9 were BCLC D only (3,4%). In terms of therapy, 67 patients (25,7%) underwent surgical/RFA treatment, 43 (16,5%) underwent TACE/TOCE/Sorafenib, while 151 (57,8%) received only symptomatic treatment.

Table1: Demography, clinical, and tumor staging information of 261 patients with HCC

ITEM	SUBGROUP	NUMBER	PERCENTAGE
Demography and clinical features			
Age	58.4 +/- 11.6		
Sex (male, female)	Male	228	87.4%
	Female	33	12.6%
Body stage	ECOG 0/1/2/1	118/135/7/1	45.2/51.7/2.7/0.4%
Presence of symptoms	Right upper quadrant pain	221	84.7%
	Fatigue	185	70.9%
	Anorexia	155	59.4%
	Not available	9	3.4%
Laboratory			
AFP	> 400 ng/ml	176	67.4%
	20 - 400 ng/ml	62	23.8%
	< 20 ng/ml	23	8.8%
SGOT, SGPT	SGOT > 40U/L	222	85.1%
	SGPT > 40 U/l	160	61.3%
Bilirubin	> 19 umol/l	103	39.5%
INR	> 1,2	79	30.3%
Albumin	< 30 g/l	53	20.3%
Platelet	< 150 g/l	73	28%
Hgb	< 120 G/l	87	33.3%
Chronic viral hepatitis	HbsAg +	192	73.6%
	Anti HCV +	25	9.6%
	HbsAg+/Anti HCV+	5	1.9%
Child - pugh	A/B/C	188/65/8	72%/24.9%/3.1%
Characteristics of tumor			
Number of tumors	1 Tumor	117	44.8%
	> = 2 Tumors	144	55.2%
Tumor size (*)	< 5cm	60	23%
	> = 5cm	201	77%

Portal vein tumor thrombus (PVTT)	Yes	131	50.2%
	No	130	49.8%
BCLC	A/B/C/D	26/58/168/9	10/ 22.2/ 64.4/ 3.4
Initial treatment	Surgery/ RFA	67	25.7%
	TACE/ TOCE/ Sorafinib	43	16.5%
	Symptomatic treatment	151	57.8%

(*) If the patient has > = 2 tumors, take the largest tumor diameter.

2. Several predicting factors for survival

Our study on 261 HCC patients who met inclusion criteria had a median survival time was 9 months with a confidence interval of 95% (7.7 - 10.3 months)

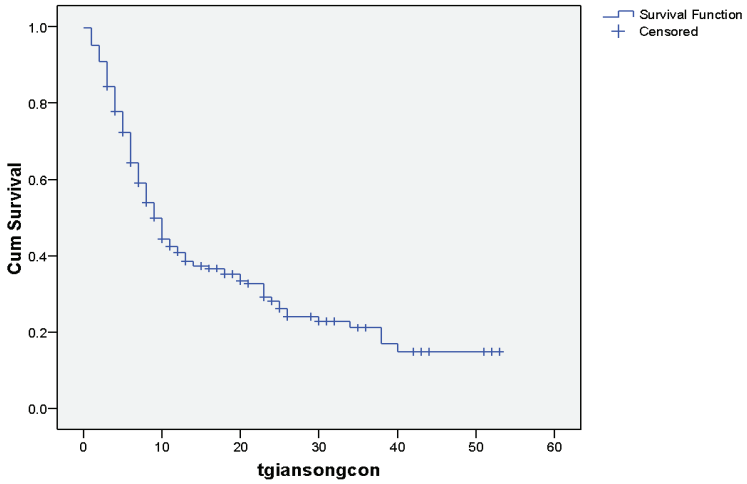

Chart 1: Total survival time of HCC patients

Table 2: Basic survival prognosis factors

Variables		N = 261	Median survival (month)	P Value
ECOG	0	118	12	0,001
	1	135	7	
	2	7	6	
	3	1	3	
AFP	< 400 ng/ml	85	11	0,17
	> = 400 ng/ml	176	9	
PVTT	yes	131	7	0,000
	No	130	13	
Child - pugh	A	188	10	0,204
	B	65	7	
	C	8	6	
Tumor size	< 5	60	14	0,02
	> = 5cm	201	8	

BCLC	A	26	34	0,000
	B	58	13	
	C	168	7	
	D	9	6	
Treatment	Surgery / RFA	67	23	0,000
	TACE/ TOCE/ Sorafenib	43	14	
	Symptomatic treatment	151	7	

Basic survival prognostic factors: univariate analysis showed that ECOG, PVTT, tumor size, BCLC, and initial treatment had significant baseline predictive value in survival time of HCC patients with $p < 0.05$ **(table 2)**. Patients with BCLC stage A had the longest survival (34 months) while in BCLC, survival was only 6 months, with $P < 0,05$. Patients receiving specific treatment (surgery, RFA, TACE, TOCE, sorafinib) had a longer survival time (23.14 months) than the symptomatic treatment group (7 months), with $p = 0.000$.

Table 3: Result of multifactor analysis

Variables group	Hazard Ratio (95% CI)	P value	P value
Tumor size	1.055	0.812	No
AFP	0.993	0.972	No
ECOG	1.187	0.277	No
PVTT	1.099	0.640	No
Child-Pugh	0.884	0.442	No
BCLC	1.471	0.034	Yes ($p < 0,05$)
Initial treatment	1.452	0.001	Yes ($p < 0,05$)

COX REGRESSION ANALYSIS

(95% confidence Interval)

In multivariate Cox model analysis, we used the meaningful variables (AFP level, ECOG, PVTT, Child - Pugh class, BCLC stage, and Initial treatment). This confirmed the identification of prognostic factors for HCC, which were significant and independent. In addition, results showed that BCLC stage (95% CI: 1.471, $P < 0.05$) and Initial treatment (95% CI: 1.452, $P < 0.05$) were independent prognostic factors for HCC.

IV. DISCUSSION

1. Clinical and laboratory characteristics

Our study on 261 HCC patients who met the inclusion criteria showed the mean age in the study was 58.4 ± 11.6 years old; the most popular age group was 40 - 60 years old, accounting for 54.8%. In this study, a male - dominated difference was 87.6%, and the male/female ratio was 6.7/1. Our research results are similar to some recent reports and studies such as the study of Tran Tien Duy (2018), the study of Abdelaziz et al (2018), and the study of Chun - yan Wang et al (2019) [1, 7, 9].

Immunomarker test results showed that up to 73.6% of patients had HBsAg (+), 9.6% of Anti - HCV (+), and 1.9% of patients were co - infected with both HBV and HCV. Thus, we realize that many patients have been infected with HBV and HCV without noticing it, leading to being untreatedand unfollowed, and it will silently result in HCC in these patients. Thus, our study is similar to other studies domestically and in many countries in East Asia and Africa with a high prevalence of HBV infection such as Sang Seok Lee in Korea (2012), Chun - yan Wang In China (2019). Countries in other regions are predominantly infected with HCV, which is consistent with the epidemiological distribution of HBV and HCV in the literature [9].

When hospitalization, performance status ECOG = 1 presented the highest figure (51.7%). Next, ECOG = 0 was 45.2%, only 0.4% of patients had ECOG = 3 and no patient had ECOG = 4. These indicators showed the performance status of the patients in the study at the time of diagnosis; most of them were still in a good physical status, similar to the study of Abdelaziz AO (2018) [7].

Regarding liver tumors: in our study, the average tumor size was 8.38 ± 4.19 cm, and nearly a half of patients had portal vein thrombosis (49.2%), while average tumor size was 5 ± 3 cm and portal vein thrombosis rate was 25.5% in the study of Chun - yan Wang et al. This shows that our patient's tumor was detected at a later stage, larger than foreign patients (see also Barcelona staging) [9].

Regarding the classification of treatment stages: In 261 patients studied, Child - Pugh classification of groups A, B, C figures were 72%, 24.9%, and 3.1%, respectively, compared to other studies such as Tran Tien Duy. Chun - yan Wang et al (China). This means that the cirrhosis rate varied across different studies, but in most studies, Child - Pugh A still accounts for the highest percentage [1, 9]. In our study, most patients with Barcelona Clinical Liver Cancer (BCLC) score C had advanced disease (64.4%). Comparison with several domestic and foreign studies shows that patients in our study are at a later stage as in the study of Chan - yan Wang et al in China (2019): Barcelona B. is the highest (40.0%), or Abdelaziz AO et al in Egypt (2018): Barcelona A (56.8%), B (34.4%) [7, 9]. This is due to the difference in the selection criteria of research subjects, sample size, the epidemiology of HCC, and the medical facilities of each country.

The treatment of liver cancer includes surgery, interventional therapy, radiation therapy, chemotherapy, biological therapy, immunotherapy, etc. [7]. Surgical resection remains the most effective treatment for HCC, and because of the biology of HCC, radiation, and chemotherapy are not sensitive. Furthermore, cirrhosis and liver dysfunction limit the dose and combination of chemotherapy. In our study, patients who received surgery or RFA had a 23 - month survival rate; those who received TOCE, TACE, Sorafenib had 14 months overall survival, higher than the group receiving only symptomatic treatment. Although the number of patients diagnosed at BCLC C stage accounted for 64.4%, BCLC D 3.4%, Child - Pugh A B was the predominant (96.9%), ECOG 0 - 1 - 2 accounted for 99.6%, ECOG 3 (0.4%) but the patients who received symptomatic treatment from the beginning accounted for 57.8%, possibly because patients have less accessibility to a specific treatment.

2. Several predicting factors for survival

It is important to clarify specifically the clinical significance and definition of prognostic and predictive factors. Although these terms sound similar, they are different. The prognostic factor is an exposure variable that is independently associated with worse clinical outcomes. In contrast, predictive factors may or may not be a prognostic factor, but it defines a population with a better or worse response to a particular treatment. Single prognostic factor analysis of survival time by Kaplan - Meier analysis in our study showed that the following factors: tumor size, body activity status, portal vein thrombosis, Barcelona stage, and initial treatment modality were significant for survival, while AFP levels and Child - Pugh classification were significant for prognosis. With the multivariable Cox model, the Barcelona stage (95% CI: 1.0 - 2.0, $p < 0.05$) and the initial treatment modality (95% CI: 1.2 - 1.8 , $p < 0.05$) are two significantly independent prognostic factors for HCC.

Overall, there are differences in our study and those of Chung - yan Wang in China (2019), Abdelaziz A.O. in Egypt (2018) on identifying prognostic factors for HCC patients. However, most studies show that stage and treatment modality are independent factors of survival. The difference in the value of prognostic factors in HCC is entirely reasonable with the current situation that there are many predictive scoring systems introduced in many countries around the world (BCLC, Okuda, CLIP), GRETCH, CUPI, TNM, JIS, biomarker - JIS) but there is no consensus on which scale has the highest predictive value to be widely applied to the whole world because that value depends on epidemiology, the pathogenesis of HCC in different countries and regions.

Regarding 2 independent prognostic factors for survival of HCC patients in our study:

The Barcelona Stage: The survival prognosis of patients with HCC depends on the Barcelona stage as following: the earlier the disease is detected (Barcelona A, B), the higher the median survival (34 months, 13 months)

Initial treatment modality: patients admitted to the hospital, naive diagnosed with HCC, initially receiving liver resection or RFA, the median survival is 23 months, 3 times higher than receiving symptomatic treatment only (7 months). For patients who TACE/TOCE or Sorafenib treated, the survival time is also greatly improved (14 months, twice as much as with symptomatic treatment only).

V. CONCLUSION

Clinical and laboratory characteristics: HCC is more common in men, with age > 50. Hepatitis B is the main risk factor and half of the patients had more than 2 tumors. About ⅔ of patients had AFP levels above 400 ng/ml and the majority of patients in Child - Pugh A and BCLC C.

Some prognostic factors for survival: The median overall survival was 9 months from the date of diagnosis. Barcelona stage and initial treatment modality are independent prognostic factors for HCC survival. The later the BCLC stage, the lower the median survival.

REFERENCES

1. Trần Tiến Duy, Mô tả đặc điểm lâm sàng, cận lâm sàng của bệnh nhân ung thư biểu mô tế bào gan. Báo cáo nghiên cứu khoa học cấp cơ sở, bệnh viện đa khoa tỉnh Ninh Thuận. Tháng 9 năm 2018.
2. Bray F, Ferlay J, Soerjomataram I, et al. 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.
3. Rawla P, Sunkara T, Muralidharan P, et al. Update in global trends and etiology of hepatocellular carcinoma, Contemp Oncol (Pozn). 2018; 22(3):141-150.
4. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma, Lancet, 2012;379(9822):1245-1255.
5. Daher S, Massarwa M., Benson A. A, et al. Current and Future Treatment of Hepatocellular Carcinoma: An Updated Comprehensive Review, J Clin Transl Hepatol, 2018;6(1):69-78.
6. Farinati F, Vitale A, Spolverato G, et al. Development and Validation of a New Prognostic System for Patients with Hepatocellular Carcinoma. PLoS Med. 2016;13(4):e1002006.
7. Abdelaziz A, Shousha H, Abdelmaksoud A. h. K, et al. A new prognostic score can predict survival after hepatocellular carcinoma treatment in a cohort of 1302 Egyptian hepatocellular carcinoma patients, European Journal of Gastroenterology & Hepatology, 2018;30:1.
8. Piñero F, Dirchwolf M, Pessôa M.G. Biomarkers in Hepatocellular Carcinoma: Diagnosis, Prognosis and Treatment Response Assessment, Cells, 2020;9(6):1370.
9. Wang C, Li S. Clinical characteristics and prognosis of 2887 patients with hepatocellular carcinoma, Medicine (Baltimore), 2019; 98(4): e14070.