Original Article

Analysis of Prognostic Factors and Treatment Outcomes for Survival in Hepatocellular Carcinoma Patients: Single Institute Experience

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Objective: Primary hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and also common in Thailand. Prognosis of HCC is very poor. Staging and clinical prognostic factors is a complex issue compared to other cancer entities. Survival depends on baseline demographic, laboratory, staging and treatment modalities. The aim of the present study was retrospectively identified prognostic factors and treatment modalities that affecting overall survival outcomes.

Materials and Methods: Retrospective chart review was performed. Demographic, laboratory and radiologic finding, treatment modalities were collected. Survival outcome was estimated using Kaplan-Meier analysis. The impact of clinical factors and therapy on survival was determined by univariate and multivariate analysis.

Results: A total of 99 patients with HCC were included. Median overall survival was 8.9 months. Based on Barcelona Clinical Liver Cancer (BCLC) staging, patients commonly presented at intermediated or late stage, compatible with 2/3 of HCC patients received Transarterial chemoembolization (TACE) therapy when compared with other therapies including best supportive care (BSC) was significantly improved survival ($p = 0.02$). Patients who had no therapy have a shorter overall survival (3.7 months). Cox-Regression univariate analysis showed younger age (equal or less than 50), abdominal pain, MELD score (more than 10), larger size of tumor (more than 5 cm.), portal vein involvement, resectability, high level of biochemistry and marker such as alkaline phosphatase (ALP), alanine aminotransferase (ALT), alpha-fetoprotein (AFP) and direct bilirubin (DB) and higher BCLC staging (B-D) were identified as clinical predictors of patient survival. Statistical analysis by multivariate showed BCLC staging, age equal or less than 50, DB more than 1 mg/dL and high ALP were significantly shortening survival.

Conclusion: The present study identified that BCLC staging could predict survival in patients with HCC-whose therapeutic outcomes showed better survival with RFA/PEI and TACE. Despite various therapies, all of the specific treatments had survival benefit comparing to BSC alone.

Keywords: Hepatocellular carcinoma, Prognostic factor, Treatment outcome, Survival

J Med Assoc Thai 2019;102(Suppl.6): 50-7
Website: http://www.jmatonline.com

Primary hepatocellular carcinoma (HCC) is the common cancer and impacts health care system worldwide. HCC is the fifth most common cancer worldwide[1] including Thailand. Around eighty percentage of HCC patients were in Asian countries due to the high prevalence of chronic hepatitis B infection[2]. In Thailand, HCC is the most common cause of morbidity and mortality in cancer patients because of poor treatment and survival outcome. In approximately 80 to 90% of all HCC patients, liver cirrhosis forms the underlying precancerosis that favors tumor development[3]. Most common risk factors were alcohol drinking and chronic hepatitis infection (B and C)[4]. A number of Thai alcohol consumer was fifth in worldwide. Chronic hepatitis B infection (CHB) is a problem in Thailand. Viral hepatitis B directly injuried and mutated to hepatocyte cells, then CHB patient also increased the risk of HCC in younger with poor prognosis[5].

Although screening, diagnosis and treatment of HCC are advance developed, overall mortality is still high. In an Early stage of HCC, most of the patients has no symptoms and diagnosis can be made in the late or advance staging of HCC. Staging of HCC is multisystemic staging because HCC is the complex disease[3]. Prognosis of survival outcome depends on tumor size and invasion, liver function test and performance status of a patient. Systematic staging that is validity and commonly used, is Barcelona clinical liver cancer (BCLC)[6]. The modality treatment in HCC is improved in this era, especially in early and intermediate stage of HCC.

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How to cite this article: Charonpongsuntorn C, Cheanklin P, Muntham D, Chommaitree P, Muangnoi P. Analysis of Prognostic Factors and Treatment Outcomes for Survival in Hepatocellular Carcinoma Patients: Single Institute Experience. J Med Assoc Thai 2019;102(Suppl.6): 50-7.

Curative treatment of HCC was surgery but the recurrent disease could occur[7]. Liver transplantation is highly benefit in this population but arrests in donor and patient performance. The modality of local therapy by Radiofrequency ablation (RFA), Percutaneous ethanol injection (PEI), Microwave coagulation therapy, Laser ablation including Transarterial chemoembolization (TACE) could be controlled by HCC progression[8]. Systemic chemotherapy had poor response in advanced HCC[9]. Targeted therapy might prolong the progression free survival and the overall survival.

The number of HCC cases in Thailand is increasing[10]. Recent study from Thailand[11] demonstrated that patients with HCC presented with late stage of disease and had a poor prognosis with shortening overall survival to only 2.1 months. Overall survival in stage I (Okuda's staging) HCC cases in Thailand was average 8 to 9 months and stage III HCC survival was only one month after diagnosis[12]. To date, the studies on prognostic factors and treatment outcomes of HCC patients applying current standard staging and guideline especially in our institution which is the referral university hospital in east region of Thailand are limited. The aim of this study was to identify prognostic factors and treatment modalities that affected overall survival outcomes of HCC patients.

Materials and Methods

A retrospective study was conducted in HRH Princess Maha Chakri Sirindhorn Medical Center (MSMC). All patients with the diagnosis of HCC in the population-based registry over a four-year period from January 2012 to December 2016 were included in the study. Those who were diagnosed with hepatocellular carcinoma and had complete chart and history reviews were eligible to enroll in this study. The diagnosis of HCC was based on the diagnostic criteria used by the American association study of liver disease (AASLD). Retrospective chart review was performed. Recorded information including demographic data, clinical manifestation, laboratory and radiologic finding, treatment modalities, complication and treatment outcome were collected. The study was conducted according to the good clinical practice guideline as well as the Declaration of Helsinki and was approved by our local ethics committee (EC073/60X).

Statistical analysis

Statistical analysis were performed using SPSS statistics version 19.0. All results were reported as frequency, median and range or mean $\pm$ standard deviation (SD) as appropriate. Categorical variables were compared using Chi-square tests or Fisher's exact test. Continuous variables were compared using the two-tailed student's t-test. Overall survival between treatment modality groups was computed using Kaplan-Meier method and compared by the log-rank test. Prognostic factors that affected survival times were computed by univariate analysis and multivariate cox-regression analysis. The different reported by hazard ratio (HR). The $p<0.05$ were considered to be statistical significance.

Results

Complete medical history and review of 99 HCC patients who were included in this study were done. Demographic characteristics were demonstrated in Table 1. Most of HCC patients were men (80.8%). Median age was more than 50 years old (68.7%). Most were poor ECOG performance status (70.9%) and were alcohol drinking (76.6%). The clinical presentation was varied but the most common presentation was abdominal pain (53.5%).

Clinical characteristics that affected survival time was younger people less than 50 years old having shortened survival (5.02 vs. 9.15 months). The patients who had abdominal presentation had longer survival time (10.24 vs. 5.02 months). Scoring system that predicted survival time was MELD score. The score higher than 10 points referred to poor survival time (5.02 vs. 9.68 months). Tumor characteristic that affected survival time were the presence of PVT (4.23 vs. 10.24 months) and tumor size of more than 5 cm (7.10 vs. 22.14 months). BCLC staging was proved that prediction of survival time. High level of biochemistry and markers (ALP, ALT, AFP and DB) were related to shorter survival time. Local therapy (RFA/PEI) and TACE were related to improved survival time.

Univariate analysis by Cox-regression method revealed younger patients (<50 years), Abdominal pain, MELD score (> 10), Larger tumor size (>5 cm), Portal vein involvement, Higher biochemistry and markers (ALP, ALT, AFP and DB), Staging by BCLC and Resectability were affected median overall survival. Multivariate analysis reviewed that BCLC staging, younger age, higher DB and ALP were significantly shortening overall survival times (Table 3).

Discussion

Hepatocellular carcinoma (HCC) was the leading cause of death in patients with cirrhosis in Thailand and worldwide. Although, there was multi-modality of HCC treatment, survival outcome of HCC patients was still poor. In recent years, Systematic scoring and staging were developed in many areas of the world such as Okuda's staging, CLIP score for prediction of prognosis in HCC patients. Barcelona Clinic Liver cancer (BCLC) staging system was approved and accepted to become the international criterion for HCC diagnosis and treatment[6]. Prognostic variable scores related to tumor size and status, liver function test and performance status[11-21]. After worldwide use of BCLC staging system, survival outcome of HCC patients was improved in multimodality of treatment. To date, Thailand had high prevalence of HCC patients and outcome of these patients were improving. There was no prior study of prognostic factors and survival outcomes in this recent year after improvement of HCC therapy.

The present study demonstrated that most patients were BCLC stage B-C that related to liver function test by

Table 1. Baseline characteristics

Baseline characteristics	Patients HCC (n = 99)
Sex	
Male	80
Female	19
Age	
≤50 years old	31
>50 years old	68
Reimbursement	
Government	38
Non-government (UC, SSS)	59
ECOG performance status	
0 to 1	28
>1	70
Smoking	
Non-smoker	29
Current	36
Ex-smoker	18
Alcohol	
No	21
Yes	69
Abdominal pain	
Yes	53
No	46
Duration	
≤1 month	46
>1 month	23
Evidence of cirrhosis	
Yes	65
No	34
Cause of cirrhosis	
Hepatitis B infection	45
Hepatitis C infection	23
Alcohol	12
Others	7
Child-Pugh score	
A	43
B	38
C	6
MELD score	
≤10	56
>10	38
Portal vein thrombosis	
Presence	30
Absence	68
Largest size	
≤5	32
>5	66
Infiltrative pattern	
Yes	20
No	67
Resectability	
Resectable	15
Unresectable	82

Table 1. Cont.

Baseline characteristics	Patients HCC (n = 99)
BCLC staging	
Stage A	16
Stage B	20
Stage C	53
Stage D	10
TB (mg/dL)	
≤1.5	67
>1.5	32
DB (mg/dL)	
≤1	73
>1	26
AST (U/L)	
≤34	8
>34	91
ALT (U/L)	
≤40	31
>40	68
ALP (U/L)	
≤126	27
>126	72
Albumin (g/dL)	
≤3.5	56
>3.5	41
PT (secs)	
≤13	16
>13	81
INR (ratio INR)	
≤1.3	77
>1.3	20
Hb (g/dL)	
≤12	53
>12	46
WBC (cells/uL)	
≤10,000	75
>10,000	24
Platelets (cells/uL)	
≤150,000	23
>150,000	76
AFP (IU/mL)	
≤250	42
>250	51
Treatment modalities	
Best supportive care	24
Surgery	4
RFA/PEI	6
TACE	61
Systemic treatment	4

child-pugh score A-B. This presentation characterized as more advanced stage or incurable disease and had slim chance to achieve curative treatment such as liver surgery or transplantation. Younger patients (less than 50 years old) might have a poor prognostic outcome. HCC in young adults was mainly resulted from CHB infection and was often diagnosed at advanced stage. Data from previous study showed that there was no survival difference in the aging of HCC diagnosis[22]. In contrast to the present study, the staging of diagnosis was advanced staging at the first presentation that might affect by survival outcomes. The presentation of abdominal pain might be a good prognosis outcome.

Table 2. Analysis of baseline characteristics affecting survival time among HCC patients

Baseline characteristics	Mortality rate/100/month	Median survival (months)	*p*-value
Sex			
Male	0.074	8.19	0.17
Female	0.047	9.15	
Age			
≤50 years old	0.116	5.02	
>50 years old	0.055	9.15	<0.01
Reimbursement			
Government	0.053	10.31	0.07
Non-Government (UC, SSS)	0.079	7.47	
ECOG performance status			
0 to 1	0.071	9.42	0.85
>1	0.065	8.62	
Smoking			
Non-smoker	0.076	7.83	0.43
Current	0.070	9.38	
Ex-smoker	0.046	8.62	
Alcohol			
No	0.079	8.00	0.46
Yes	0.061	8.92	
Abdominal pain			
Yes	0.051	10.24	<0.01
No	0.101	5.02	
Duration			
≤1 month	0.068	7.83	0.96
>1 month	0.076	8.92	
Evidence of cirrhosis			
Yes	0.064	8.00	0.58
No	0.075	8.92	
Cause of cirrhosis			
Hepatitis B infection	0.063	8.19	0.88
Hepatitis C infection	0.074	9.42	
Alcohol	0.060	8.92	
Others	0.052	14.57	
Child – Pugh score			
A	0.061	10.24	0.11
B	0.082	6.08	
C	0.135	0.69	
MELD score			
≤10	0.055	9.68	<0.01
>10	0.108	5.02	
Portal vein thrombosis			
Presence	0.122	4.23	<0.01
Absence	0.054	10.24	
Largest size			
≤5	0.041	22.14	<0.01
>5	0.088	7.10	
Infiltrative pattern			
Yes	0.087	4.52	0.17
No	0.059	9.15	
Resectability			
Resectable	0.032	30.28	0.01
Unresectable	0.079	8.00	
BCLC staging			
Stage A	0.022	33.81	<0.01
Stage B	0.068	11.04	
Stage C	0.084	7.11	
Stage D	0.248	2.91	

Table 2. Cont.

Baseline characteristics	Mortality rate/100/month	Median survival (months)	*p*-value
TB (mg/dL)			
≤1.5	0.059	9.61	0.09
>1.5	0.091	5.05	
DB (mg/dL)			
≤1	0.058	9.6198	<0.01
>1	0.117	4.760	
AST (U/L)			
≤34	0.048	5.950	0.37
>34	0.069	8.925	
ALT (U/L)			
≤40	0.048	10.41	0.03
>40	0.079	6.51	
ALP (U/L)			
≤126	0.037	22.34	<0.01
>126	0.089	7.14	
Albumin (g/dL)			
≤3.5	0.083	7.14	0.20
>3.5	0.058	9.62	
PT (secs)			
≤13	0.049	10.31	0.18
>13	0.077	8.56	
INR (ratio INR)			
≤1.3	0.065	8.92	0.17
>1.3	0.097	7.14	
Hb (g/dL)			
≤12	0.063	8.62	0.57
>12	0.073	8.92	
WBC (cells/uL)			
≤10,000	0.065	9.09	0.37
>10,000	0.073	2.67	
Platelets (cells/uL)			
≤150,000	0.044	14.11	0.06
>150,000	0.078	8.00	
AFP (IU/mL)			
≤250	0.053	9.61	0.03
>250	0.084	6.51	
Treatment modalities			
Best supportive care	0.108	3.70	0.02
Surgery	0.071	3.33	
RFA/PEI	0.020	30.28	
TACE	0.063	9.61	
Systemic treatment	0.136	3.23	

Explanation of this fact might be that the presentation of clinical symptoms such as abdominal pain would lead a patient to visit a physician at a hospital and making an early diagnosis of HCC. Furthermore, the investigational study of genetic alteration in young-onset HCC should be considered. There were no previous studies about clinical presentation as prognostic factors of survival. Our study was retrospectively collected of the clinical presentation of HCC patients and demonstrated that abdominal presentation as an individual predictive factor for prolong survival. Because half of HCC patients had no symptoms and were diagnosed with imaging surveillance. Abdominal pain might be the factor that improved survival due to early diagnosis. Tumor status and liver biochemistry such as high MELD score, large size of tumor (>5 cm), Portal vein involvement and abnormal liver function test were individual prognosis markers for survival outcomes in HCC patients same as described in the previous studies[3,20,21]. Liver biochemistry was parted of the scoring system such as Okuda's staging or CLIP score. Higher ALT or bilirubin were the poor prognosis factors. Our previous systematic analysis demonstrated the same outcome that bilirubin was a poor outcome factor for HCC prognosis and treatment outcome[3,20,21]. There was no previous study reported on ALP as a prognosis marker of HCC. This study showed ALP as an individual prognostic factor for a shorter survival. ALP level was elevated in a space occupying lesion

Table 3. Cox-Regression analysis of survival in HCC patients

Factor	Univariate			Multivariate		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (≤50)	1.86	1.17 to 2.96	<0.01	2.36	1.38 to 4.02	<0.01
Largest size (>5)	1.99	1.24 to 3.20	<0.01			
Abdominal pain	1.86	1.21 to 2.86	<0.01			
AFP (>250 IU/mL)	1.60	1.03 to 2.49	0.03			
ALP (>126 U/L)	2.22	1.33 to 3.69	<0.01	1.88	1.07 to 3.31	0.02
ALT (>40 U/L)	1.62	1.02 to 2.59	0.04			
DB (>1 mg/dL)	1.87	1.16 to 3.03	0.01	1.93	1.08 to 3.44	0.02
MELD score (>10)	1.83	1.18 to 2.84	<0.01			
Portal vein thrombosis	2.20	1.39 to 3.48	<0.01			
Resectability (unresectable)	2.32	1.19 to 4.53	0.01			
BCLC staging						
A	1			1		
B	2.80	1.25 to 6.25	0.01	2.65	1.11 to 6.32	0.02
C	3.50	1.70 to 7.20	<0.01	3.55	1.63 to 7.71	<0.01
D	9.76	3.84 to 24.8	<0.01	10.71	3.83 to 29.89	<0.02
Treatment modalities						
Best supportive care	1					
Surgery	0.61	0.18 to 2.05	0.42			
RFA/PEI	0.19	0.05 to 0 .64	<0.01			
TACE	0.55	0.33 to 0.91	0.02			
Systemic treatment	1.02	0.35 to 3	0.95			

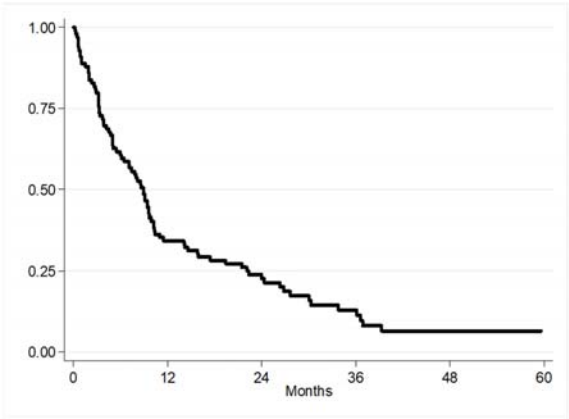

Figure 1. Kaplan-Meier survival estimate of overall survival in HCC patients.

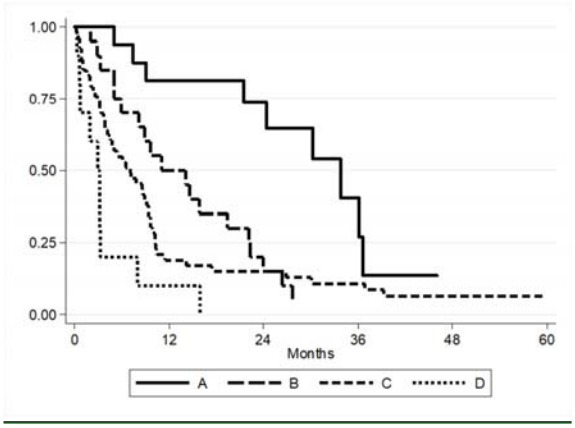

Figure 2. Kaplan-Meier survival estimate of overall survival comparison BCLC staging in HCC patients.

in the liver, intrahepatic metastasis or bone metastasis. This fact might explain that ALP was a higher burden in HCC and resulted in the survival outcome. BCLC staging was the validity scoring system to predict survival outcome in HCC. Worldwide reports and systematic reviewed studies demonstrated the validity of this scoring systems. In Thailand, our study was the first study that showed the validity of BCLC scoring systems as the prognostic tool for prediction of the outcomes as reported in the previous studies (Figure 2). In term of treatment outcome, the patients who received cancer therapy had longer survival than those who received best supportive care. Local therapy such as TACE or RFA/PEI had the better survival due to staging of disease. While many patients with BCLC stage C such as portal vein thrombosis or distant metastasis were contraindicated for TACE, this treatment modality in our institute and the reimbursement of targeted therapy was limited. Our institute protocol was recommended TACE in some patients.

Median overall survival in the present study was 8.9 months. Previous HCC studies in Thailand and Malaysia revealed that HCC patients in this region had the poor outcomes with an overall survival only for 2 months[11]. Updated HCC studies[10,26] in Thailand revealed the median

survival of 10.5 months as reported in our study. This data revealed that the survival outcome of HCC patients was improved due to the use of diagnosis test, interventional therapy and systemic treatment in this region including Thailand. Although, most of the patients in this study were in BCLC stage B-C overall survival was improved regardless of the staging. However, patient with BCLC stage D who had best supportive care intent to have poor survival outcomes due to poor liver function tests, performance status and reimbursement problem in Thailand.

The benefit of this study was that this study revealed the univariate and the multivariate analysis that were not be reported before in Thailand. Individual factors that affected survival were aging, ALP level, bilirubin and BCLC staging. The limitation of the study was that it was a single institution study and retrospective study with small numbers of HCC patients. The numbers of patients who had systemic therapy in this study was small because of the limitation of reimbursement for targeted therapy at that period. Further study with more patients, multicenter and prospective design is required to clarify validity of this factor–and to predict model analysis in overall population in Thailand.

Conclusion

The present study identified that BCLC staging could predict survival in patients with HCC. Therapeutic outcomes with RFA/PEI and TACE showed the better survival. The prognostic factors analyzed by multivariate analysis that affected survival outcomes were younger patients, high level of ALP and bilirubin. Despite various therapies, all of the specific treatments showed survival benefit comparing to BSC alone.

What is already known on this topic?

The prognostic factors that affected survival in HCC patients depended on various factors. Important factors from the previous studies were performance status, staging of disease, liver biochemistry, tumor marker and treatment modalities.

What this study adds?

The present study confirmed the validity and the value of these factors through statistical analysis. BCLC staging was the valuable staging to predict HCC prognosis in Thai population. In addition, younger HCC patients had poor survival outcomes that were needed to further exploration in genetic or molecular alterations.

Acknowledgements

The authors would like to thank all colleagues in the Department of Internal Medicine, Faculty of Medicine, Srinakharinwirot University especially the Hepatocellular excellent center-team, Asst. Prof. Dr. Piyanant Chommaitree and Dr.Panunat muangnoi for their invaluable help and encouragement throughout the course of this research. Finally, the authors were most appreciated for the participation of all patients in this research.

Potential conflicts of interest

The authors declared no conflicts of interests.

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