ORIGINAL ARTICLE

Demographics and Treatment Outcomes of Hepatocellular Carcinoma: A Retrospective Study in Single Tertiary Care Hospital

Panitpong Maroongroge, MD[1], Asawin Sudcharoen, MD[2], Piyakorn Poonyam, MD[2], Nutthawut Laoarphasuwong, MD[2], Aritach Trakulbanlue[3], Natthanon Ngamwat[3], Peeraya Tangkavachiranon[3], Pitchawee Wannakrairoj[3], Kitsarawut Khuancharee, PhD[4], Piyanant Chonmaitree, MD[2]

[1] Department of Radiology, Faculty of Medicine, Srinakharinwirot University, Nakhon Nayok, Thailand; [2] Department of Medicine, Faculty of Medicine, Srinakharinwirot University Ongkharak Campus, Nakhon Nayok, Thailand; [3] Medical student, Faculty of Medicine, Srinakharinwirot University, Nakhon Nayok, Thailand; [4] Department of Preventive and Community Medicine, Faculty of Medicine, Srinakharinwirot University, Nakhon Nayok, Thailand

Background: Hepatocellular carcinoma (HCC) is one of the most common cancers in Thailand. There are various treatment modalities for HCC. Most patients with HCC are diagnosed at an advanced stage resulting in limited treatment options and poor outcomes.

Objective: To assess the demographic characteristics and outcomes of patients with HCC at HRH Princess Maha Chakri Sirindhorn Medical Center.

Materials and Methods: A retrospective study was conducted, involving patients aged 18 years and older diagnosed with HCC between January 2011 and August 2021. All clinical information and laboratory and radiologic findings were collected.

Results: Among 538 HCC patients, 430 were males, with a mean age of 58.8 years. Hepatitis B was the most common risk factor at 48.9%, and 92.4% of patients had cirrhosis. Abdominal pain was the predominant presenting symptom. Only 5.2% of patients were identified through the surveillance program. Asymptomatic patients identified through the surveillance program showed better survival rates compared to those who were not detected through the program, with a median survival of 37.2 months versus 27.6 months, respectively (p=0.035). Patients were classified by the Barcelona Clinic Liver Cancer (BCLC) stage as follows, 6.2% at stage 0, 31.0% at stage 1, 23.0% at stage 2, 30.1% at stage 3, and 9.7% at stage 4. Portal vein thrombosis was presented in 26.9% of the patients. Treatment modalities included resection for 3.5%, radiofrequency ablation for 3.2%, transarterial chemoembolization for 71.2%, targeted therapy for 1.3%, chemotherapy for 4.5%, and best supportive care for 9.3%. The median survival time was 14.4 months. Factors associated with mortality included the year of diagnosis between 2011 and 2016, presence of diabetes mellitus (DM), chronic kidney disease (CKD), abdominal pain, weight loss, jaundice, Child-Turcotte-Pugh (CTP) score of B or C, BCLC stage 4, infiltrative tumor type, tumor size larger than 5 cm, tumor rupture, presence of metastasis, alpha-fetoprotein (AFP) levels equal to or greater than 200 IU/mL, and not receiving specific treatment.

Conclusion: HCC patients continued to have a poor prognosis. Patients identified through the surveillance program had better survival rates than those who were not, but only a minority of patients were detected through this program. Therefore, encouraging the surveillance program is crucial.

Keywords: Hepatocellular carcinoma; Demographics; Treatment outcome

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Hepatocellular carcinoma (HCC) is the leading cancer-related mortality worldwide. Liver cancer is the second most deadly and fifth most common solid malignancy. The estimated incidence of liver cancer was 905,677 cases and death from liver cancer was 830,200 cases in 2020[1]. The incidence of liver cancer is predicted to increase by 55% in the next two decades[1]. Liver cancer patients in Thailand accounted for 4.2% of liver cancer in Asia[2]. In Thailand, liver cancer is the most common cancer in males and the fourth most common cancer in females[3]. HCC is the most common liver cancer. The highest incidence rates occur in Southeast Asia and sub-Saharan Africa[4]. It is more common in males than females. Major risk factors for HCC are hepatitis B, hepatitis C, chronic alcohol consumption, and non-alcoholic fatty liver disease. The Barcelona Clinic Liver Cancer (BCLC) staging is the most widely used staging system for HCC in Western

Correspondence to:

Chonmaitree P.

Department of Medicine, Srinakharinwirot University, Ongkharak Campus, Nakhon Nayok 26120, Thailand.

Phone: +66-37-395085 ext. 60617

Email: piyanant_n@yahoo.co.th

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countries, which includes an integrated assessment of liver function, tumor stage, and performance status[5]. The current treatment options for HCC are liver resection, ablation with percutaneous ethanol injection, radiofrequency ablation (RFA), microwave ablation, and laser ablation, liver transplantation, transarterial chemoembolization (TACE), targeted therapy, chemotherapy, and best supportive care (BSC). Expert panels advocate for multidisciplinary care of patients with HCC comprising specialists in multiple fields including gastroenterologists, intervention radiologists, radiologists, oncologists, and surgeons. Previous studies in Thailand had reported median survival times of 11.5 months for stage I, 2.6 months for stage II, and 0.7 months for stage III according to Okuda's tumor staging[6]. Another study indicated an overall median survival of 9.0 months for treated patients and 2.3 months for untreated patients[7]. However, there is no available data on the treatment outcomes of HCC in this region of Thailand, and the previous studies were conducted up to ten years ago. The objective of the present study was to determine the demographics and treatment outcomes of patients with HCC in a single tertiary care center.

Materials and Methods

The present study was a retrospective study was conducted at the HRH Princess Maha Chakri Sirindhorn Medical Center (MSMC), Nakhon Nayok, Thailand between January 2011 and August 2021. MSMC is a tertiary care hospital located in the central region of Thailand, offering a 500-bed facility and well-equipped for all treatment modalities except liver transplantation. The study included all Thai patients with HCC, identified using the International Classification of Disease (ICD) 9 and 10 codes from the medicine and surgical departments. Data was collected from electronic medical records.

HCC was diagnosed based on histological findings or radiological modalities according to European Association for Study of the Liver (EASL) guidelines[4]. The exclusion criteria were age younger than 18 years, hepatocholangiocarcinoma, refusal of treatment, and lack of identification card number to check the date of death. The following information were recorded, demographics as age and gender, body mass index (BMI), comorbidities, history of alcohol consumption or smoking, cause of HCC, year of treatment, clinical features, Child-Turcotte-Pugh (CTP) score, BCLC stage, type of tumor, number of HCC, tumor size, portal vein thrombus (PVT), PVT type, history of rupture, metastasis, alpha-fetoprotein (AFP) level, and treatments. Comorbidities, such as cerebrovascular accident and end-stage renal disease, were ascertained through the use of ICD-9 and ICD-10 codes. Alcohol consumption was characterized as drinking more than 20 g/day in women and 30 g/day in men while smoking was defined as any dose and duration of cigarette smoking. Treatments were categorized as resection, RFA, TACE, targeted therapy, chemotherapy, and BSC. Patients were included in a routine follow-up program, and loss to follow-up was defined as the last visit date being more than 12 months before the date of death. Dates of death were obtained from the Civil Registration Office. The present study was approved by the Ethics Committee of Srinakharinwirot University, Thailand (SWUEC/E-283/2564) and conducted in accordance with the Declaration of Helsinki.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range) and compared using ANOVA. Categorical variables were expressed as frequency and percent and analyzed by chi-square or Fisher's exact-test.

BMI was categorized into three groups according to the World Health Organization (WHO) Asian-Pacific classification as underweight (BMI of less than 18.5 kg/m^2), normal weight (BMI of 18.5 to 22.9 kg/m^2), and overweight (BMI of 23 kg/m^2 or more)[8]. The optimal cutoff value for AFP in predicting prognosis in HCC patients was not universally defined. However, according to the previous study, a cutoff of 200 IU/mL was utilized[9].

The survival analysis with the life table method, survival, and the log rank test were calculated. Univariate and multiple Cox-proportional hazards regression models were used to estimate treatment effect as hazard ratio (HR) and 95% confidence interval. All statistical analyses were performed using Stata, version 14 (StataCorp LP, College Station, TX, USA). All analyses were considered statistically significant at p-value less than 0.05.

Results

The baseline characteristics of patients with HCC

Baseline characteristics are summarized in Table 1. Five hundred thirty-eight patients were included and most were male. Their mean age was 58.8 years. BMI of HCC patients less than 18.5, 18.5 to 22.9, and equal or more than 23 were 6.9%, 35.3%, and 57.8%, respectively. Chronic hepatitis B

Table 1. Baseline characteristics

	n=538
Year of diagnosis; n (%)	
2011-2013	81 (15.1)
2014-2016	137 (25.5)
2017-2019	235 (43.7)
2020-2021	85 (15.8)
Age (years); mean±SD	58.8±11.7
Male/female; n (%)	430/108 (80.0/20.0)
BMI (kg/m^2) (n=412); n (%)	
18.5 to 22.9	190 (35.3)
<18.5	37 (6.9)
≥23	311 (57.8)
Comorbidity; n (%)	
Diabetes mellitus	159 (29.6)
Hypertension	204 (37.9)
Cerebrovascular disease	36 (6.7)
Chronic kidney disease	56 (10.4)
Alcohol consumption; n (%)	393 (73.1)
Smoking; n (%)	289 (53.7)
Cause; n (%)	
Hepatitis B	262 (48.9)
Hepatitis C	126 (23.5)
Alcohol	196 (36.6)
NAFLD	52 (9.7)
Others	13 (2.4)
Symptom; n (%)	
No	163 (30.3)
Abdominal pain	242 (45.0)
Abdominal distension	96 (17.8)
Weight loss	131 (24.4)
Jaundice	67 (12.5)

	n=538
Symptom (continued); n (%)	
Gastrointestinal bleeding	28 (5.2)
Cirrhosis; n (%)	496 (92.4)
CTP score A/B/C; n (%)	353/143/36 (66.4/26.9/6.8)
BCLC stage	
0	33 (6.2)
1	167 (31.0)
2	124 (23.0)
3	162 (30.1)
4	52 (9.7)
Mass/infiltrative/mixed type; n (%)	471/48/19 (87.6/8.9/3.5)
Single/multiple tumors; n (%)	248/290 (46.1/53.9)
Tumor size (cm) (n=315); n (%)	
<2	45 (8.4)
2 to 5	164 (30.5)
>5	329 (61.2)
PVT (n=532); n (%)	143 (26.9)
Bland/tumor PVT type (n=147); n (%)	10/137 (6.8/93.2)
Rupture; n (%)	54 (10.2)
Metastasis; n (%)	103 (19.2)
AFP (IU/mL); n (%)	
<200	272 (54.4)
≥200	228 (45.6)
Therapy; n (%)	
Best supportive care	50 (9.3)
Resection	19 (3.5)
Radiofrequency ablation	17 (3.2)
TACE	383 (71.2)
Targeted therapy	7 (1.3)
Chemotherapy	24 (4.5)

BMI=body mass index; NAFLD=non-alcoholic fatty liver disease; CTP=Child-Turcotte-Pugh; BCLC=Barcelona Clinic Liver Cancer; PVT=portal vein thrombosis; AFP=alpha-fetoprotein; TACE=transarterial chemoembolization; SD=standard deviation

infection was the most common cause at 48.9%, and 92.4% showed evidence of liver cirrhosis. Among non-cirrhotic patients, 50% had chronic hepatitis B, while non-alcoholic fatty liver disease (NAFLD) was found in 10% of the patients and the cause was unknown in 30% of patients. Eight patients were coinfected with hepatitis B and hepatitis C. The common presenting symptoms included abdominal pain for 45.0% and weight loss for 24.4%. Twenty-eight patients (5.2%) were detected through the surveillance program. Among patients with cirrhosis, CTP scores were A in 66.4%, B in 26.9%, and C in 6.8%. Six point two percent of the patients were classified as BCLC stage 0 or very early, 31.0% as stage 1 or early, 23.0% as stage 2 or intermediate, 30.1% as stage 3 or advanced, and 9.7% as stage 4 or terminal. The majority of HCC cases were mass-forming at 87.6% while 8.9% were being infiltrative, and 3.5% were being mixed. Multiple tumors were more common than single tumors at 53.9% versus 46.1%. Tumor size was greater than 5 cm. in 61.2% of cases, while 38.9% were 5 cm. or less. PVT was presented in 26.9% of patients and most commonly as a tumor type with 93.2%. Approximately 10% of patients had ruptured HCC. Metastasis was observed in 103 patients with 46 to the lung, 45 to lymph nodes, 11 to bone, 6 to the adrenal gland, and 4 to other locations. Regarding AFP levels, 54.4% of patients had AFP lower than 200 IU/mL. About 84% of patients received specific treatment. Regarding treatment modalities, patients underwent hepatic resection, RFA, TACE, targeted therapy,

chemotherapy, and BSC at 3.5%, 3.2%, 71.2%, 1.3%, 4.5%, and 9.3%, respectively. Forty-eight patients did not receive any treatment, including 12, 4, and 32 patients in BCLC stage 1, 2, and 3, respectively.

The impact of hospitalization year on patient survival

The overall survival time was 14.4 months. One hundred eighty-seven patients or 34.8% were lost to follow-up. The 1-, 2-, 3-, and 5-year survival rates of HCC patients were equal to 52.2%, 39.3%, 31.1%, and 20.3%, respectively (Table 2). Patients were divided into two groups based on the periods of 2011 to 2016 and 2017 to 2021. The 1-, 2-, 3- and 5-year overall survival rates for these two periods were 49.1% and 54.4%, 36.2% and 41.4%, 27.5% and 33.7%, 16.1% and 24.2%, respectively. There was a significant improvement in overall survival over the period (p=0.022) (Figure 1). The percentage of HCC diagnoses made through surveillance increased from 6.9% to 8.6% between 2011 and 2016, and 2017 and 2021, respectively.

The impact of clinical variables on patient survival

From Table 2, patients with a history of alcohol consumption had significantly higher mortality rates compared to those without alcohol consumption (p=0.003). Patients with a history of smoking had a median survival of 12 months, significantly lower than patients without a history of smoking (p=0.013). Asymptomatic patients had better survival than symptomatic patients. Among asymptomatic patients, 28 individuals were detected through the surveillance program, and they exhibited superior survival compared to those not identified through the program (median survival of 37.2 months versus 27.6 months, respectively, p=0.035). The median survival time was 25.2, 6.0, and 1.2 months for patients with CTP score A, B, and C, respectively. A log-rank test revealed statistically significant differences among these groups (p<0.001). Patients with BCLC stage 0, 1, 2, 3, and 4 had median survival times of 55.2, 40.8, 18.0, 6.0, and 1.2 months, respectively (p<0.001). The five-year survival rates for stages 0, 1, 2, 3, and 4 were 48.1%, 40.5%, 12.4%, 6.9%, and 0%, respectively. Regarding the type of HCC, mass-forming, infiltrative, and mixed types had a median survival of 18.0, 1.2, and 6.0 months, respectively. Mass-forming HCC had significantly longer survival than infiltrative and mixed types (p<0.001). The median survival of a single HCC was higher than multiple HCCs at 26.4 versus 9.6 months (p<0.001).

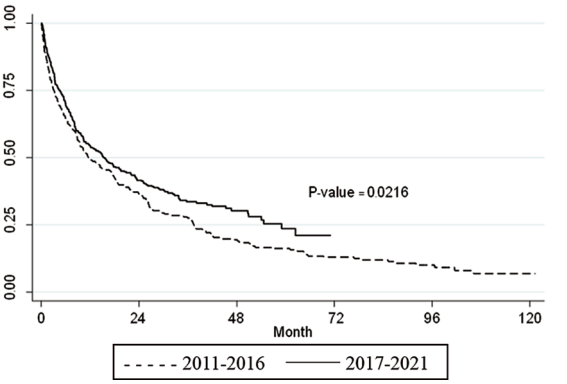

Figure 1. Plots of Kaplan-Meier estimates survival of a group of patients between the year 2011-2016 and 2017-2021.

Tumor size of less than 2 cm, 2 to 5 cm and larger than 5 cm had a median survival of 50.4, 36.0, and 7.2 months, respectively (p<0.001). HCC without PVT had significantly higher median survival than HCC with PVT at 25.2 versus 3.6 months (p<0.001). The median survival of ruptured HCC was lower than HCC without rupture significantly at 4.8 versus 15.6 months (p<0.001). HCC with metastasis had lower cumulative survival than HCC without metastasis at 3.6 versus 18 months (p<0.001). Patients with AFP levels of less than 200 IU/mL had better survival than patients with AFP of 200 IU/mL or more at 26.4 versus 7.2 months (p<0.001).

The impact of different modes of therapy on patient survival

Regarding the type of treatment, hepatic resection, RFA, TACE, targeted therapy, chemotherapy, and BSC had median survival of 51.6, 48.0, 21.6, 4.8, 6.0, and 1.2 months, respectively. The median survival rates of HCC patients differed significantly based on the therapeutic modality (p<0.001) (Table 2).

The factors associated with the overall survival of HCC patients

Factors associated with mortality are presented in Table 3.

In univariate analysis, several factors were significantly associated with mortality, including the year of diagnosis, alcohol consumption, smoking, symptomatic presentation, CTP score, BCLC stage, tumor characteristics for type, number, and size, presence of PVT, tumor rupture, presence of metastasis, AFP levels, and not receiving specific treatment. However, gender, diabetes mellitus, and etiology were not found to be associated with mortality.

Table 2. Overall survival of HCC patients

Characteristics	n	Median time	95% CI	Overall survival				p-value
				1-year	2-year	3-year	5-year	
Overall	538	14.4	0.9 to 1.5	52.2	39.3	31.1	20.3	-
Year of diagnosis								0.022
2011-2016	218	12.0	0.7 to 1.5	49.1	36.2	27.5	16.1	
2017-2021	320	15.6	1.0 to 1.7	54.4	41.4	33.7	24.2	
Alcohol consumption								0.003
No	145	22.8	1.2 to 2.5	59.3	48.3	37.6	30.8	
Yes	393	12.0	0.8 to 1.3	49.5	35.8	28.6	16.5	
Smoking								0.013
No	249	19.2	1.2 to 2.2	57.4	46.1	36.1	21.2	
Yes	289	12.0	0.7 to 1.2	47.6	33.8	26.6	18.6	
Symptom								
No	163	40.8	2.8 to 4.3	79.8	68.0	55.6	38.8	<0.001
Abdominal pain	242	7.2	0.5 to 0.8	39.3	25.2	18.9	12.6	<0.001
Abdominal distension	96	3.6	0.2 to 0.7	30.2	19.6	13.7	11.2	<0.001
Weight loss	131	8.4	0.5 to 0.9	38.2	26.6	19.9	14.6	0.001
Jaundice	67	2.4	0.1 to 0.4	23.9	11.9	10.4	3.5	<0.001
CTP score								<0.001
A	353	25.2	1.6 to 2.5	66.3	50.6	40.3	28.3	
B	143	6.0	0.3 to 0.7	30.8	20.9	15.6	7.4	
C	36	1.2	0.1 to 0.1	2.8	0.0	0.0	0.0	
BCLC stage								<0.001
0	33	55.2	2.4 to 6.4	84.8	75.8	65.7	48.1	
1	167	40.8	2.7 to 4.9	77.8	64.0	53.7	40.5	
2	124	18.0	1.1 to 2.1	61.3	42.5	30.6	12.4	
3	162	6.0	0.4 to 0.7	28.4	15.9	11.4	6.9	
4	52	1.2	0.1 to 0.9	1.9	0.0	0.0	0.0	
Type								<0.001
Mass	471	18.0	1.2 to 1.9	58.2	43.8	35.0	22.7	
Infiltrative	48	1.2	0.1 to 0.2	8.3	6.3	6.3	0.0	
Mixed	19	6.0	0.2 to 0.6	15.8	10.5	0.0	0.0	
Tumor number								<0.001
Single	248	26.4	1.5 to 3.1	64.5	52.3	44.2	31.6	
Multiple	290	9.6	0.6 to 0.9	42.7	28.2	20.0	10.9	
Tumor size (cm)								<0.001
<2	45	50.4	2.8 to 5.8	86.7	73.3	63.6	44.4	
2 to 5	164	36.0	2.2 to 4.2	76.2	60.8	50.2	33.7	
>5	329	7.2	0.5 to 0.7	35.6	23.9	17.2	10.4	
PVT								<0.001
No	389	25.2	1.7 to 2.5	64.3	50.5	40.3	25.9	
Yes	149	3.6	0.2 to 0.5	19.6	10.5	7.6	5.8	
Rupture								<0.001
No	482	15.6	1.0 to 1.6	55.9	41.8	32.9	22.1	
Yes	56	4.8	0.2 to 0.7	28.6	17.9	15.8	3.9	
Metastasis								<0.001
No	434	18.0	1.3 to 2.0	58.9	45.1	35.9	23.9	
Yes	103	3.6	0.2 to 0.5	23.3	14.4	10.3	4.9	
AFP (IU/mL)								<0.001
<200	272	26.4	1.8 to 2.8	68.0	53.2	43.0	38.4	
≥200	228	7.2	0.5 to 0.8	38.6	26.6	20.4	11.8	
Type of treatment								<0.001
Best supportive care	50	1.2	0.1 to 0.4	2.0	0.0	0.0	0.0	
Resection	19	51.6	0.4 to 5.4	68.4	57.9	57.9	49.6	
Radiofrequency ablation	17	48.0	3.0 to 5.9	88.2	82.4	82.4	46.3	
TACE	383	21.6	1.5 to 2.2	64.2	47.4	36.1	23.0	
Targeted therapy	7	4.8	0.2 to 0.6	28.6	28.6	0.0	0.0	
Chemotherapy	24	6.0	0.3 to 0.9	16.7	8.3	8.3	8.3	

BMI=body mass index; NAFLD=non-alcoholic fatty liver disease; CTP=Child-Turcotte-Pugh; BCLC=Barcelona Clinic Liver Cancer; PVT=portal vein thrombosis; AFP=alpha-fetoprotein; TACE=transarterial chemoembolization; CI=confidence interval

Table 3. Univariate and multiple Cox regression analysis

Variables	Overall survival (n=369)			
	HR (95% CI)	p-value	AHR (95% CI)*	p-value
Year of diagnosis				
2011-2016	1.00		1.00	
2017-2021	0.79 (0.65 to 0.97)	0.022	0.58 (0.4 to 0.9)	0.033
Comorbidity				
Diabetes mellitus	0.8 (0.7 to 1.0)	0.104	0.4 (0.2 to 0.8)	0.014
Hypertension	0.9 (0.7 to 1.1)	0.415	1.7 (0.8 to 3.6)	0.934
Cerebrovascular disease	0.9 (0.6 to 1.3)	0.512	0.1 (0.04 to 0.5)	0.528
Chronic kidney disease	0.8 (0.6 to 1.1)	0.203	3.0 (1.7 to 5.4)	<0.001
Alcohol consumption				
No	1.00		1.00	
Yes	1.4 (1.1 to 1.8)	0.003	1.5 (0.7 to 3.1)	0.258
Smoking				
No	1.00		1.00	
Yes	1.3 (1.1 to 1.6)	0.014	0.9 (0.5 to 1.6)	0.736
Symptom				
No	0.4 (0.3 to 0.5)	<0.001	0.5 (0.2 to 1.4)	0.207
Abdominal pain	1.8 (1.5 to 2.2)	<0.001	1.9 (1.0 to 3.7)	0.044
Abdominal distension	1.9 (1.5 to 2.4)	<0.001	1.8 (0.9 to 3.5)	0.086
Weight loss	1.4 (1.2 to 1.8)	0.001	0.4 (0.2 to 0.6)	<0.001
Jaundice	2.6 (1.9 to 3.4)	<0.001	2.5 (1.2 to 5.1)	0.009
Gastrointestinal bleeding	0.8 (0.5 to 1.3)	0.420	0.3 (0.1 to 1.1)	0.071
CTP score				
A	1.00		1.00	
B-C	2.8 (2.3 to 3.4)	<0.001	3.1 (1.6 to 5.6)	<0.001
BCLC stage				
0	1.00		1.00	
1	1.2 (0.7 to 2.1)	0.385	1.5 (0.5 to 4.1)	0.435
2	2.4 (1.4 to 4.1)	<0.001	2.1 (0.7 to 6.4)	0.202
3	4.6 (2.8 to 7.7)	<0.001	1.8 (0.6 to 5.6)	0.308
4	30.7 (17.3 to 54.5)	<0.001	15.1 (1.4 to 57.6)	0.024
Type				
Mass	1.00		1.00	
Infiltrative	4.5 (3.3 to 6.1)	<0.001	2.6 (1.6 to 3.9)	<0.001
Mixed	3.1 (1.9 to 4.9)	<0.001	1.7 (1.0 to 3.1)	0.056
Tumor number				
Single	1.00		1.00	
Multiple	1.9 (1.6 to 2.4)	<0.001	1.5 (0.8 to 2.8)	0.223
Tumor size (cm)				
<2	1.00		1.00	
2 to 5	1.3 (0.8 to 2.0)	0.249	0.6 (0.3 to 1.6)	0.329
>5	3.5 (2.3 to 5.2)	<0.001	6.7 (1.7 to 26.6)	0.007
PVT				
No	1.00		1.00	
Yes	3.2 (2.6 to 3.9)	<0.001	1.4 (0.9 to 2.2)	0.076
Rupture	1.9 (1.4 to 2.6)	<0.001	2.2 (1.1 to 4.8)	0.040
Metastasis	2.5 (1.9 to 3.1)	<0.001	1.8 (1.0 to 3.2)	0.039
AFP (IU/mL)				
<200	1.00		1.00	
≥200	2.0 (1.6 to 2.4)	<0.001	1.3 (1.1 to 1.6)	0.039
Treatment				
Best supportive care	1.00		1.00	
Specific treatment	0.07 (0.05 to 0.09)	<0.01	0.1 (0.07 to 0.2)	<0.001
Type of treatment				
Best supportive care	1.00		1.00	
Resection	0.03 (0.01 to 0.06)	<0.001	0.04 (0.01 to 1.2)	0.061
Radiofrequency ablation	0.02 (0.01 to 0.05)	<0.001	0.03 (0.1 to 6.2)	0.658
TACE	0.06 (0.04 to 0.08)	<0.001	0.09 (0.03 to 0.2)	<0.001
Targeted therapy	0.12 (0.05 to 0.29)	<0.001	0.27 (0.05 to 1.4)	0.123
Chemotherapy	0.13 (0.08 to 0.22)	<0.001	0.18 (0.06 to 0.5)	0.002

CTP=Child-Turcotte-Pugh; BCLC=Barcelona Clinic Liver Cancer; PVT=portal vein thrombosis; AFP=alpha-fetoprotein; TACE=transarterial chemoembolization; HR=hazard ratio; AHR=adjusted hazard ratio; CI=confidence interval

* Adjusted for age, CTP score, BCLC stage, tumor number, tumor size, and PVT Global test=0.7899

In multivariate analysis, the year of diagnosis between 2011 and 2016, presence of DM, CKD, abdominal pain, weight loss, jaundice, CTP score B and C, BCLC stage 4, infiltrative tumor, tumor size larger than 5 cm, tumor rupture, presence of metastasis, AFP levels equal to or greater than 200 IU/mL, and not receiving specific treatment remained as independent predictors of overall mortality.

Discussion

This retrospective study involved 538 patients from tertiary hospitals between 2011 and 2021, with a longer follow-up period compared to the previous studies in Thailand[6,7,10]. HCC is a prevalent cancer worldwide, particularly in Asia[11], where its high incidence is attributed to the prevalence of hepatitis B and C[2]. Among Asian countries, the lowest survival rates have been reported in the Philippines, India, Singapore, and Thailand[12]. In the present study, the number of HCC patients continuously increased from 2011 until the COVID-19 pandemic, in 2020 and 2021, which may affect the referral system. This increasing number of patients may be partly attributed to the surveillance program, as the proportion of HCC patients detected through the program has risen. The authors' center initiated the surveillance program for high-risk patients before 2012. The incidence rate of HCC was directly correlated with age, peaking at 70 years[4], whereas in Thailand, the peak incidence was 45 years[13]. Similar to the previous studies[4,6,7,14], HCC was common in males, with a male-to-female ratio of 4:1, and hepatitis B virus was the most common risk factor of HCC at 48.9%. Males had a higher rate of hepatitis B infection and alcohol intake than females[15-17]. Cirrhosis was found in 92.4% of HCC patients in the present study, consistent with global data[18]. The overall survival of HCC patients was 14.4 months in the current study, longer than the median survival reported in previous studies in Thailand, which was 2.3 to 10.5 months[6,7,10]. Compared with meta-analysis from Asian countries, the 1-, 3-, and 5-year survival rates in the present study were higher at 52.2% versus 34.8%, 31.1% versus 19.0%, and 20.3% versus 18.1%, respectively[12]. The higher proportion of early-stage HCC patients in the present study compared to previous studies might be attributed to the surveillance program, offering a plausible explanation for these findings. Moreover, a multidisciplinary care team played an important role in optimizing the management of HCC. The results of the present study showed that the survival rate has increased from between 2011 and 2016 to between 2017 and 2021. The rate of mortality has continuously declined over time in Asian studies[12], suggesting improvements in healthcare quality, including screening, available effective treatment, and multidisciplinary teams. In the authors' hospital, they have a multidisciplinary team including surgeons, interventional radiologists, hepatologists, and oncologists.

In the present study, HCC patients with DM exhibited higher mortality rates than those without DM. DM was associated with morphologically advanced lesions and advanced liver disease, as well as an increase in postoperative hepatic decompensation[19,20]. Data on HCC outcomes in CKD patients were scarce. Patients on long-term dialysis had higher risk of liver cancer[21]. HCC patients with stage 4 and 5 chronic kidney disease had higher mortality than stage 1 and 2 chronic kidney disease[22]. Survival rates after liver resection in patients with CKD varied among studies, with some showing no significant difference compared to patients without CKD, while others reported significantly lower survival rates[23-26]. In the present study, HCC patients with CKD exhibited significantly higher mortality rates than those without. This suggests that CKD may indeed serve as a poor prognostic factor in HCC. Several mechanisms could contribute to this association, including immune dysfunction, impaired DNA repair mechanisms, and decreased antioxidant defense in CKD patients. However, further studies are needed to fully understand the impact of CKD on patient prognosis in the context of HCC.

The present study showed that the prognosis became significantly worse as the CTP score increased. This finding was consistent with the previous studies[22,27-29]. CTP score B and C may preclude some patients with HCC from treatment. The BCLC staging system is the most commonly utilized, encompassing prognostic variables concerning tumor status, liver function, and performance status[30]. It has been externally validated in studies, supporting its reliability and generalizability[31,32]. In the present study, BCLC stage 4 was associated with significantly higher mortality rates than stage 0.

Infiltrative HCC is considered uncommon, accounting for 7% to 13% of all HCC cases, and was found in only 8.9% of cases in the present study. This form of HCC is often subtle and difficult to detect, and it exhibits a poorer prognosis compared to the mass-forming type[33,34]. Following the EASL guidelines, targeted therapy was recommended for patients diagnosed with intermediate-stage infiltrative

HCC[4]. Tumor size and the presence of metastasis have all been associated with an increased risk of poorer survival outcomes[6,9,35]. Ruptured HCC is a potentially life-threatening condition. The acute phase of ruptured HCC had a mortality rate of 23.5% to 75%[36-38]. HCC with rupture had significantly higher mortality than HCC without rupture in the present study. Elevated levels of AFP were significantly associated with increased mortality, however, there is currently no universally accepted AFP threshold associated with prognosis[6,39,40]. The present study results underscore the prognostic relevance of AFP levels.

Treatment was an independent prognosticator of survival, consistent with other datasets[6,7,10,35]. The proportion of patients who received hepatic resection, RFA, and targeted therapy as primary treatment were low. Targeted therapy is recommended for advanced-stage HCC. However, only a few patients in the present study received this treatment. This discrepancy may be due to the high cost of targeted therapy, which many patients cannot afford without health insurance coverage.

The prognosis of HCC is complex, with multiple factors influencing patient survival. The present study provides insights into the impact of variables on the survival of HCC patients. Previous studies had identified age, gender, tumor size, number of tumors, disease stage, CTP score, PVT, metastasis, AFP, and type of treatment as predictors of survival[6,7,35,41-43]. Careful consideration of these factors is crucial for improving treatment outcomes in HCC patients.

HCC surveillance plays a crucial role in improving early tumor detection and survival rates. Surveillance strategies, such as ultrasound with or without AFP, are recommended for high-risk patients by the EASL[14], the American Association for the Study of Liver Diseases (AASLD)[44], and the Asian Pacific Association for the Study of the Liver (APASL) guidelines[45]. In the present study, only 5.2% of HCC patients were detected through surveillance, and the proportion of patients diagnosed with very early and early-stage HCC was only 37.2%. These findings underscore the importance of encouraging high-risk patients to participate in surveillance programs to detect HCC at early stages, thereby improving overall survival rates.

There are limitations inherent to its design. First, this is a single-center study with a small sample size, which may limit the generalizability of the findings. Second, the retrospective design of the analysis prevents the establishment of causality. Lastly, lack of baseline data on comorbidities. Despite these limitations, the present study was able to adjust for most variables pertinent to HCC outcomes.

Conclusion

The mortality rate of HCC has consistently decreased over time. Prognostic factors of HCC included comorbidities with DM and CKD, symptoms at presentation, CTP score, BCLC stage, type of tumor, size of tumor, presence of rupture tumor, metastasis, AFP levels, and receiving specific treatment.

What is already known on this topic?

HCC is the leading cause of cancer-related fatalities worldwide, including in Thailand.

There are various treatment modalities for HCC, underscoring the importance of a multidisciplinary team in ensuring comprehensive care.

What does this study add?

More than half of the patients with HCC were diagnosed at stage 2 to 4.

The surveillance program may enhance the prognosis of patients with HCC and should be strongly encouraged.

Prognostic factors for HCC include comorbidities (DM, CKD), symptoms at presentation, CTP score, BCLC stage, tumor type, tumor size, presence of rupture, metastasis, AFP levels, and receipt-specific treatment.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

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Conflicts of interest

The authors declare no conflict of interest.

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