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Clinical analysis, treatment patterns, and long-term outcomes of Hepatocellular carcinoma in Thailand: A multidisciplinary approach

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ABSTRACT

Background: Liver cancer, particularly hepatocellular carcinoma (HCC), is the most prevalent cancer in Thailand and globally. However, comprehensive hospital-based survival data remains limited.

Objectives: The study aimed to ascertain the prevalence, impact of treatment modalities on survival among hepatocellular carcinoma (HCC) patients, and reasons for long-term survival.

Methods: A retrospective study was conducted using medical records of 1,221 HCC patients aged ≥18 years from January 2014 to December 2018. Data were extracted from electronic health records using ICD-10 code C22.0. Long-term survival was defined as surviving ≥5 years. Cox proportional hazard regression analysed clinical characteristics and mortality risk.

Results: A total of 1,221 HCC patients were analysed, with 80.80% mortality during follow-up and median survival of 1.25 years (95%CI: 1.09-1.37). The 5-year and 10-year survival rates were 22.6% (95%CI: 20.30-24.99) and 10.92% (95%CI: 8.84-13.25), respectively. Multivariable analysis showed better survival for females (adjusted HR=0.82; 95%CI: 0.69-0.97) and poorer outcomes with bilateral involvement versus right lobe (adjusted HR=1.34; 95%CI: 1.11-1.62). Surgical resection yielded the highest 5-year survival (58.48%; 95%CI: 52.44-64.03) compared to other treatments, while 29.5% received no treatment.

Conclusion: Surgical resection provided superior survival outcomes. Female gender, right lobe tumour location, and Civil Servant Medical Benefit Scheme (CSMBS) coverage were favourable prognostic factors. Enhanced multidisciplinary care integration is essential to improve treatment accessibility and survival outcomes.

Keywords: HCC, Liver cancer, Mortality, Payment, Treatment modalities

1. Introduction

Liver cancer is the sixth most common cancer diagnosis and the fourth most common cause of cancer deaths in the world. Hepatocellular carcinoma (HCC) accounts for 75-80% of all primary cancers and is responsible for an increasing number of cancer-related deaths. It is estimated that 72% of cases occur in Asia (with half of newly diagnosed HCC cases worldwide reported from China), 10% in Europe, 7.8% in Africa, 5.1% in North America, 4.6% in Latin America, and 0.5% in Oceania [1, 2]. In the United States, there were over 38,000 HCC cases in 2020, projected to rise over 56,000 by 2030, with the incidence expected to increase over the next 10-15 years, resulting in approximately 47,000 deaths per year in Europe [3]. In Thailand, liver and bile duct cancer rank as the most common cancer in males (14,293 cases, 23.9 %) and the second most common cancer in females (6,378 cases,10.1%). The mortality rate for liver cancer was 25.2 per 100,000 persons [4].

Liver cancer, particularly hepatocellular carcinoma (HCC), poses a significant threat in Thailand, with mortality rates rising faster than for any other cancer. Various studies have identified key risk factors for HCC including the Hepatitis B virus (HBV), hepatitis C virus (HCV), cirrhosis, aflatoxin-contaminated food, heavy alcohol consumption, tobacco smoking, obesity, and metabolic syndrome [5, 6]. The survival rate for HCC is quite low in all countries. In fact, HCC is typically diagnosed late in its course, with a median survival in the advanced stage of HCC following diagnosis of approximately 6 to 11 months [7, 8]

HCC and overall survival varied according to the treatment option. The effects of treatment and survival rate have seen only limited improvements in HCC in Thailand. It is well known that previous studies have often reported cholangiocarcinoma, which is predominantly found in Thailand. In addition, HCC is frequently reported in the liver and bile duct [3, 9]. This study discusses the factors relevant to the duration of survival in these primary HCC patients after diagnosis. The method of treatment, the tumour's general prognostic factors, and the tumour's own characteristics were found to determine the duration of survival. Therefore, the purpose of the present study was to analyse and compare the prognostic factors between 5-year survival groups and to explore the treatment pattern for long-term survival.

2. Methods

2.1 Study Population

Patients diagnosed with HCC and/or treated at the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand between 2014 and 2018 were included in a retrospective database after hospital admission. Patients' baseline characteristics were reviewed, and the data were gathered from the hospital's medical electronic record system using the ICD-10 coding system and patients' files. Patients' baseline characteristics were reviewed. Cancer histopathology, tumour site, and extent of disease were assessed according to the International Classification of Disease for Oncology, Third Edition Site code C22.0 and Histology Code 8170 [10]; and the Barcelona Clinic Liver Cancer (BCLC) system was applied [11]. The healthcare service schemes were divided into three groups: 1) Civil Servant Medical Benefit Scheme (CSMBS), 2) Social Security Scheme (SSS), and 3) Universal Health Coverage (UHC). Treatment modalities included transcatheter arterial chemoembolization (TACE), radiofrequency ablation (RFA), hepatic resection, chemotherapy, palliative care, and others. Overall survival (OS) was defined as the time from the date of diagnosis to the date of death or the date of the last follow-up. Follow-up examinations were completed by October 31, 2024. The status of each patient and the cause of death were verified using the records of the Bureau of Registration Administration (BORA).

This study was a retrospective analytic study utilizing an existing hospital-based cancer registry, which included all 1,221 patients diagnosed and treated during the study period. Therefore, we did not perform a prior sample size calculation. However, to ensure the adequacy of our sample, we conducted a post-hoc power analysis.

2.2 Statistical Analysis

To determine the correlation of survival and treatment modalities received, clinical characteristics, treatment, and survival outcome were retrospectively collected. Patients' baseline characteristics were summarized using descriptive statistics, and patients' clinical characteristics were defined as categorical variables. To minimize the impact of missing data, we attempted to retrieve all relevant information from the electronic medical records. Furthermore, a post-hoc power analysis was conducted to confirm the adequacy of our sample size, mitigating concerns related to missing data.

Cumulative survival percentages were estimated using the Kaplan-Meier method. The statistical significance of the differences in cumulative survival was evaluated using the log-rank statistic for homogeneity. P-value < 0.05 indicates a significant difference, and 95% confidence intervals (CIs) were computed for survival proportions and rates. Long-term survival of HCC patients was defined as survival of 5 years or longer. A Cox proportional hazard regression model was used to evaluate the significance of the associations between other factors and death, which are represented as hazard ratios (HRs) and the 95% confidence interval (95%CI). Statistical analysis was performed using STATA 16.0 (College Station, Texas 77845, USA)

3. Results

3.1 Demographic and Treatment Modalities

A total of 1,221 cases of HCC were registered in the 5-year period between January 1, 2014, and December 31, 2018. The majority of patients were male, with 917 (75.1%) cases were males and 304 (24.8%) were females resulting in a male-to-female ratio of 3.02:1. The median (range) age of those enrolled was 62 (17-97) years. One-third of patients were between 55 and 64 years old at the time of diagnosis. Regarding the type of payment, the most common healthcare system was the CSMBS, followed by UHC and SSS. Baseline characteristics are summarized in Table 1. Initial treatment modality for HCC detected between 2014 and 2018 were assessed. Patients with advanced stage or end-stage HCC comprised the majority in the study, with an extremely small number of cases in the early stage. The initial treatment modalities were trans arterial chemoembolization (TACE/TOCE) in 39.0% and resection in 22.7% of patients. The proportion of patients who rejected treatment remained high at 28.8%. Additionally, the proportion of patients who received only supportive care as the initial treatment was 0.7% (see Figure 1).

Table 1: Baseline characteristics Hepatocellular carcinoma patients (n=1,221)

Patient Characteristics	Number (n)	Percentage (%)
Gender		
Male	917	75.10
Female	304	24.90
Age at diagnosis (years)		
≤49	154	12.61
50-59	355	29.07
60-69	394	32.27

Patient Characteristics	Number (n)	Percentage (%)
70-79	238	19.50
80+	80	6.55
Mean age at diagnosis (SD)	62.1 (11.21)	
Median (IQR)	62 (15)	
Type of Payment		
CSMBS	335	27.44
SSS	61	5.00
UC	271	22.19
Other	554	45.37
Barcelona staging		
I	160	13.10
III	460	37.70
III	417	34.10
IV	184	15.10
Position of lesion		
Right lobe	559	45.80
Left lobe	167	13.70
Both lobe	166	13.60
Unknown	329	26.90
Time on Therapy (years)		
Mean (SD)	1.89 (1.81)	
Median (Min: Max)	1.23 (0.002, 6.90)	
Initial treatment		
Resection	277	22.69
TACE/TOCE	477	39.07
Systemic treatment	108	8.84
Palliative RT	8	0.65
Reject/Referred	351	28.75

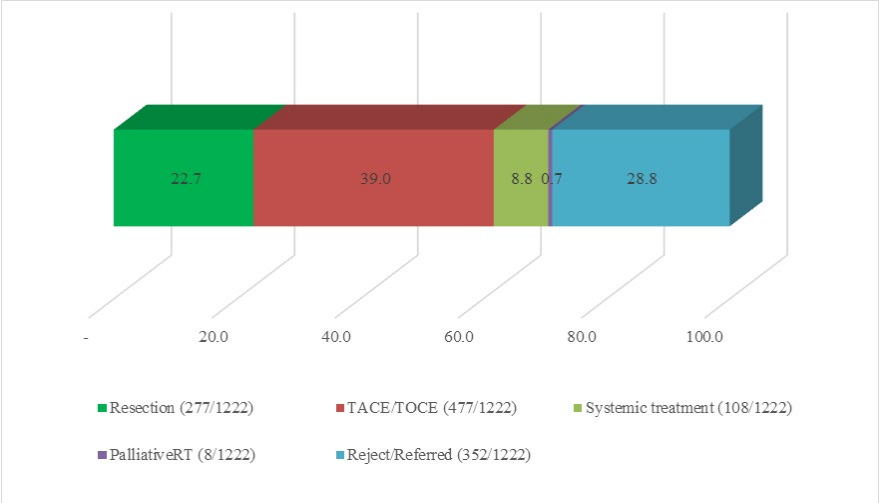


Figure 1: Initial treatment modality for HCC detected between 2014 and 2018

3.2 Survival and Factor Associations

At the conclusion of the study, with a median (interquartile range) follow-up period of 14.4 (44.4) months, there were 988 deaths, accounting for 80.8% of cases. Our research highlighted that the primary cause of death

among HCC patients was attributed to the disease itself or the effects of liver cancer (59.1%), followed by infection and sepsis (6.8%), liver cirrhosis (4.9%), bleeding (1.8%), heart failure (1.0%), and other causes (8.2%). Regarding the follow-up of 3276.6 person-years, the mortality rate was 32.04 per 100 person-years, and the median survival time (interquartile range) was 1.25 (0.33-4.38) years. The 1, 2, 3, 4, 5 and 10-year OS rates were 54.87 (95%CI: 50.04-57.62), 41.5 (95%CI: 38.7-44.2), 32.27 (95%CI: 29.66-34.35), 26.7 (95%CI: 24.1-29.3), 22.6 (95%CI:20.30-24.99), and 10.92 (8.84-13.25), respectively. Overall survival by variable factors is shown in Figure 2. Among genders, the OS rate was significantly lower when compared with females. The survival analysis by gender showed significant differences (P=0.001), with males having a median survival of 1.12 years (95%CI: 0.95-1.27) and 5-year OS of 21.7% (95%CI: 19.09-24.42), while females demonstrated better outcomes with median survival of 1.85 years (95%CI: 1.34-2.23) and 5-year OS of 30.33% (95%CI: 20.59-30.33). Regarding staging and the side of liver cancer, patients with advanced stage and bilateral lobe of liver cancer still led to a poor survival rate. The 5-year survival rates were 3.8% (95%CI: 1.69-7.30) in the stage IV group. The 5-year survival rate is quite low when compared with any stage. For the side of HCC, the best survival outcome was found in HCC patients who had right lobe involvement, and poor survival was observed in the left lobe and bilateral lobe (see Table 2). Kaplan-Meier analysis showed that the following factors significantly affected the prognosis of HCC (P<0.05): Gender, type of treatment, staging, side, and treatment modalities (Table 2).

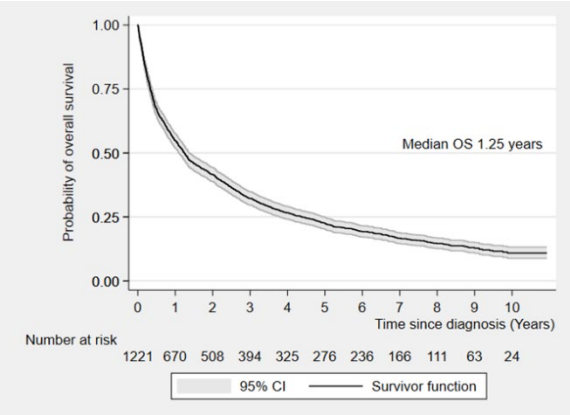
Table 2: The overall survival relative survival Hepatocellular carcinoma patients (n=1,221)

Factors	Median Survival (Year, 95%CI)	Overall survival rates (%, 95%CI)				P-value
		1-YR	3-YR	5-YR	10-YR	
All	**1.25 (1.09-1.37)**	**54.87 (50.04-57.62)**	**32.27 (29.66-34.35)**	**22.60 (20.30-24.99)**	**10.92 (8.84 -13.25)**	
Gender						0.002
Male	1.12 (0.95-1.27)	52.45 (49.17-55.63)	30.75 (27.79-33.76)	21.70 (19.09-24.42)	8.43 (6.08-11.25)	
Female	1.87 (1.34-2.23)	67.35 (56.46-67.35)	42.25 (31.44-42.25)	30.33 (20.59-30.33)	17.00 (12.75-21.77)	
Age at diagnosis (years)						0.360
17-49	0.65 (0.44-1.32)	46.75 (38.71-54.38)	31.82 (24.63-39.23)	25.32 (18.76-32.39)	15.01 (8.15-23.81)	
50-59	1.33 (0.97-1.82)	55.21 (49.30-59.70)	33.52 (27.60-37.30)	23.38 (18.30-27.10)	13.08 (9.35-17.45)	

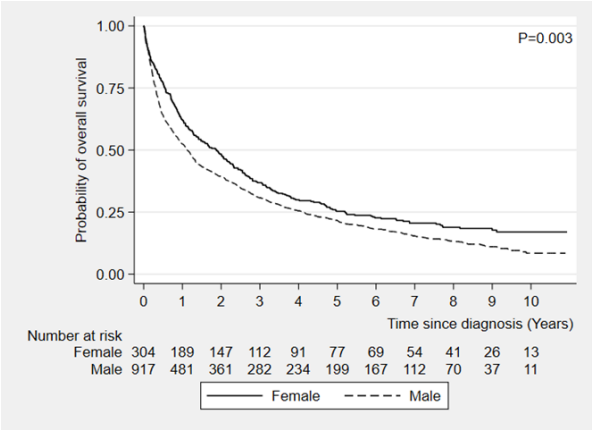
Factors	Median Survival (Year, 95%CI)	Overall survival rates (%, 95%CI)				P-value
		1-YR	3-YR	5-YR	10-YR	
60-69	1.37 (1.16-1.93)	59.39 (54.37-64.05)	33.76 (29.13-38.44)	22.84 (18.83-27.1)	8.53 (5.41-12.52)	
70-79	1.23 (0.84-1.65)	53.36 (46.82-59.46)	31.09 (25.32-37.02)	21.01 (16.09-26.39)	11.25 (7.45-15.91)	
80+	1.04 (0.70-1.42)	51.25 (39.84-61.54)	23.75 (15.12-33.49)	17.50 (10.13-26.54)	5.83 (1.80-13.41)	
Type of Payment						0.004
CSMBS	1.88 (1.33-2.55)	62.09 (56.66-67.04)	40.60 (35.32-45.8)	28.96 (24.19-33.87)	13.37 (9.53-17.86)	
SSS	1.85 (1.00-2.61)	63.93 (50.57-74.56)	32.79 (21.46-44.58)	19.67 (10.85-30.41)	6.56 (1.68-16.25)	
UC	1.54 (1.23-2.02)	59.04 (52.94-64.63)	32.47 (26.97-38.08)	19.56 (15.08-24.48)	10.39 (6.85-14.77)	
Other	0.90 (0.73-1.01)	47.47 (43.26-51.56)	27.08 (23.44-30.83)	20.58 (17.32-24.04)	9.99 (6.62-14.18)	
Staging						<0.001
I	7.55 (5.76-8.6)	83.13 (76.36-88.1)	71.88 (64.22-78.17)	62.50 (54.51-69.48)	42.12 (32.98-50.96)	
III	2.06 (1.65-2.43)	65 (60.45-69.16)	39.13 (34.66-43.56)	25.87 (21.96-29.94)	11.14 (7.78-15.18)	
III	0.80 (0.64-1.06)	46.04 (41.20-50.75)	20.62 (16.89-24.63)	11.99 (9.09-15.31)	1.80 (0.27-6.54)	
IV	0.37 (0.30-0.44)	25.00 (19-31.43)	7.07 (3.96-11.37)	3.80 (1.69-7.30)	1.36 (0.10-5.39)	
Laterality						<0.001
Right	1.48 (1.25-2.00)	57.96 (53.75-61.93)	34.88 (30.95-38.84)	24.87 (21.36-28.51)	11.97 (7.86-16.99)	
Left	1.69 (1.09-2.313)	60.48 (52.64-67.43)	36.53 (29.28-43.79)	22.16 (16.2-28.71)	11.34 (6.68-17.35)	
Bilateral	0.61 (0.37-0.97)	42.17 (34.6-49.53)	16.27 (11.12-22.27)	9.04 (5.29-13.99)	4.46 (1.82-8.96)	
Initial treatment						<0.001
Resection	6.20 (5.19-6.93)	89.89 (85.70-92.91)	72.92 (67.28-77.76)	58.48 (52.44-64.03)	30.98 (24-37.86)	
TACE/ TOCE	1.53 (1.29-1.87)	63.31 (58.82-67.46)	29.98 (25.93-34.13)	17.61 (14.34-21.16)	5.45 (2.66-9.69)	
Systemic treatment	1.01 (0.64-1.37)	50.93 (41.16-59.88)	22.22 (14.93-30.44)	12.04 (6.76-18.94)	5.47 (1.95-11.71)	
Reject/ Referred	0.22 (0.19-0.27)	17.83 (14.07-21.96)	6.96 (4.64-9.91)	4.74 (2.87-7.28)	3.00 (1.51-5.32)	

The impact of different treatment modalities on patient prognosis. Patients who underwent liver resection had better outcomes than patients initially treated with other treatment modalities, with a median OS was 6.20 years (95%CI: 5.19-6.93). Analysis based on therapy received shown that the OS of patients who received treatment was better than that of patients who rejected treatment or were referred to another hospital

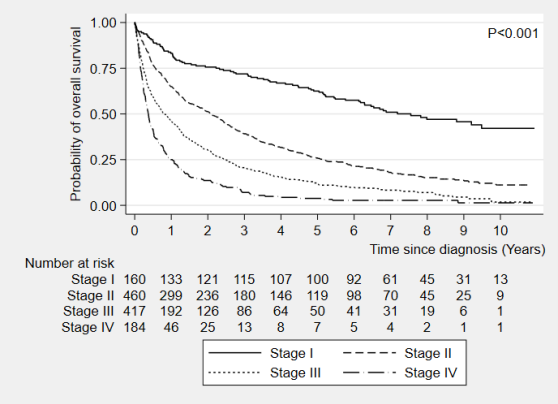
(P<0.001). Among the 477 patients who continued receiving TACE/TOCE, the OS was better than the 108 patients who underwent systemic treatment (median OS 1.53 vs. 1.01 years, P = 0.021) (Figure 2).



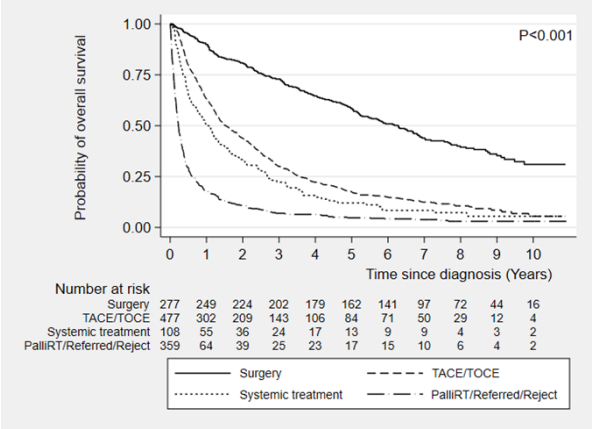
2A) Overall survival



2B) OS by gender



2C) OS by staging



2D) OS by treatment modalities

Figure 2: Overall survival by variable factors

Staging consistently plays a critical role in determining treatment outcomes. Patients undergoing surgery demonstrated the highest survival rates across all disease stages, with particularly notable 5-year overall survival rates in stage 1 (78.5%) and stage 2 (51.43%). In contrast, systemic treatment showed survival rates comparable to TACE/TOCE in the earlier stages but exhibited a significant decline in stages 3 and 4, with a 5-year survival rate of 16.67% in stage 4 (Table 3).

Table 3: Percent 5-Year Overall Survival (OS) in HCC Patients by Disease Stage and Initial Treatment

Initial Treatment	5-Year Overall Survival (%, 95%CI)			
	Stage 1	Stage 2	Stage 3	Stage 4
Surgery	78.50 (69.45-85.16)	51.43 (41.50-60.48)	44.44 (31.00-57.04)	9.09 (0.54-33.29)

TACE/TOCE	33.33 (14.88-53.07)	23.05 (17.97-28.51)	11.18 (6.91-16.59)	5.77 (1.51-14.36)
Systemic treatment	33.33 (0.90-77.41)	13.89 (5.08-27.05)	7.84 (2.51-17.22)	16.67 (4.12-36.54)
Palliative/Referred/Rejected	27.59 (13.06-44.28)	5.26 (1.71-11.89)	2.65 (0.87-6.19)	0.97 (0.09-4.77)

Proportional hazard ratio analysis showed that several variables were significant prognostic factors for HCC including gender, type of payment, tumour side and staging. This study found that an independent factor predicting favourable prognosis was coverage under the CSMBS. Patients covered under the SSS and UHC experienced adjusted hazard ratios of 1.34 (95% CI: 0.96-1.86) and 1.28 (95% CI:1.04-1.57), respectively, compared with those covered by the CSMBS. Surgery had the best survival rate compared to patients who received other treatments. Patients whose first treatment was systemic treatment had a 2.18 times higher risk of death compared to patients whose first line of treatment was liver surgery. Figure.3 showed the estimated hazard ratios for all-cause mortality.

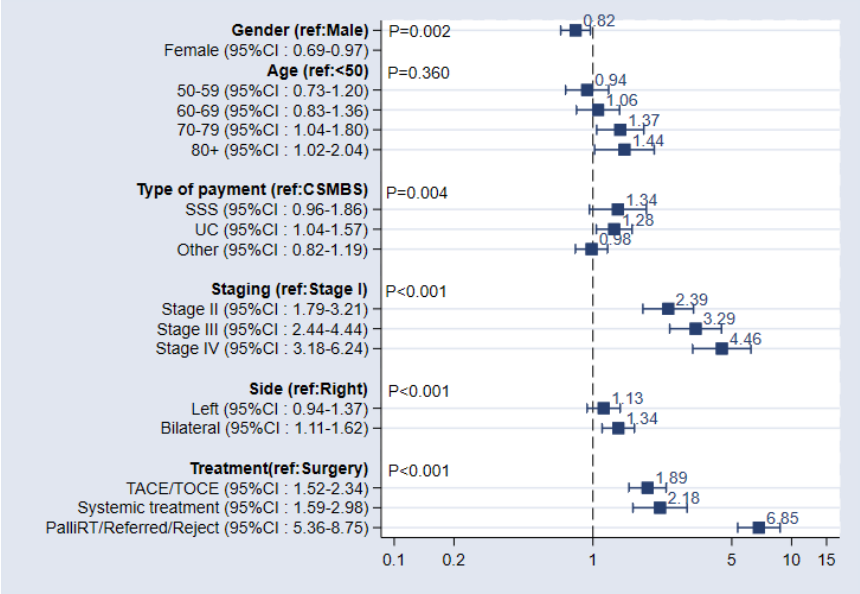


Figure 3: Adjusted hazard ratios with 95% confidence intervals for death from HCC using cox proportional hazard regression model

4. Discussion

In our study, the mean 5-year OS rate for all HCC patients was 22.60%. Although the total number of patients in this study was quite large (1,221 cases), our finding yielding a 5-year OS rate comparable to those reported in

various regions, including the United States (6.6%), Poland (10.5%), the SEER database (21.5%) and China (16.8%). However, our recorded rate fell below those reported in Japan and Korea. This disparity could be attributed to the distinctive nature of our institution - a medical school and tertiary referral health care centre which routinely handles a significant influx of advanced cancer cases referred from across the nation. Consequently, our study cohort comprised a notable proportion of patients presenting with advanced disease. In contrast, Japan and South Korea have highly efficient screening systems for high-risk populations, such as individuals with hepatitis B or C infection, liver cirrhosis, or a family history of liver cancer. These screening programs typically include abdominal ultrasound and serum alpha-fetoprotein (AFP) measurement, facilitating the early detection of hepatocellular carcinoma (HCC). Notably, in Japan, more than 62.5% of HCC cases are detected at an early stage. [8, 12-15].

As observed in our finding, trans arterial chemoembolization (TACE) emerged as the most commonly utilized treatment modality, with no patients receiving radiofrequency ablation (RFA) as their initial treatment. Curative surgical interventions demonstrated the highest long-term survival rates compared to transcatheter arterial chemoembolization (TACE), trans arterial oily chemoembolization (TOCE), and systemic treatments. This study demonstrated that the 5-year overall survival rates in patients who received hepatic resection, TACE/ TOCE, and systemic treatment were 58.48% (95% CI: 52.44-64.03), 17.61% (14.34-21.16), and 12.04% (6.76-18.94), respectively. The overall survival rate for patients receiving systemic treatment typically tends to be lower compared to those who undergo surgery. Consequently, chemotherapy becomes the primary treatment modality for such cases, complemented by essential supportive care [16]. This study identified that 8% of patients did not undergo primary treatment and instead received only palliative care. This may be because some patients were referred to Ramathibodi Hospital with severe symptoms, such as recurrent disease, to the extent that mainstream treatments would not provide meaningful benefits. In such cases, treatment might only increase healthcare costs and patient suffering. As a result, some patients refused further treatment and were referred back to their original hospitals for continued palliative care [17]. This study found that tumour side and patients' health

coverage were significant prognostic factors. Thus, coverage under the CSMBS and being on the right side were significant prognostics. patient who was covered under the CSMBS had a 0.83 times lower risk of death compared with those covered by the SSS (P=0.085). For patients under CSMBS, these individuals may have better access to treatment, particularly chemotherapy, compared to others, potentially leading to differences in overall survival rates [18].

Through our study, an examination of the male-female ratio of the deaths from liver cancer revealed that there were 753 males to 304 females, and the OS rate is notably lower in males (HR = 0.82 times; 95%CI: 0.69-0.97, P = 0.022) compared to females. It was conceivable that in Thailand, men consume more alcohol than women, leading to a higher incidence of liver disease among men compared to women. With the trend of alcohol consumption among women in Thailand reaching parity with that of men, it is anticipated that the incidence of liver disease and cancer may become comparable between genders in the future [19, 20].

Cancer stage and tumour location emerged as significant prognostic factors. Tumour location analysis revealed that patients with right lobe involvement showed better survival outcomes compared to those with bilateral involvement (HR=1.34; 95%CI: 1.11-1.62, P=0.002). This finding aligned with previous studies suggesting that unilateral tumours, particularly in the right lobe, often allow for more successful surgical interventions due to better anatomical accessibility and preservation of functional liver tissue. In contrast, bilateral involvement typically indicated more extensive disease, limiting treatment options and resulting in poorer outcomes. The primary cause of death is often attributed to patients being admitted at the symptomatic stage, which typically occurs towards the end of the disease progression. This study found that more than 80% of patients who died were at stage IV or had an unknown stage. The 5-year OS of patients with stage IV was 3.80% (95%CI: 1.69%-7.3%), imposed a 4.46 times higher risk compared to patients with stage I. Positive survival outcomes for patients with early-stage disease have been improving. However, over the past 5 years, the proportion of new patients diagnosed at an early stage remains low, with more than 60% presenting with cancer at an advanced stage that cannot be assessed. Other regions, including Europe (2000), the United States (2001), Japan (2002), Korea (2003), and Taiwan (2004), have implemented national

policies for screening and early detection of HCC [21-24]. In Thailand, a national policy for HCC screening was launched in 2015, but it has not yet been adequately comprehensive [25]. Increasing screening for liver cancer is likely to lead to the detection of more cases at early stages. Coupled with appropriate treatment guidelines, this could result in prolonged survival rates for patients. As per our findings, there are several strengths as well as limitations. Significant strengths include the considerable volume of HCC cases included, the extensive follow-up duration, and the comprehensive staging of the disease.

Conversely, the limitations stem from the retrospective nature of the study, reliance on data from a single centre, which is a medical school, potentially leading to an overestimation of results.

5. Conclusion

Hepatocellular carcinoma (HCC) is frequently encountered. Future research may prioritize investigating treatment outcomes to deepen insights and facilitate the selection of optimal treatment modalities. This could involve delving into socioeconomic factors and associated costs to develop treatment guidelines suitable for the specific context of the country in the coming years. Patients with stage III-IV disease often have a poor prognosis, highlighting the need to strengthen prevention and screening to increase early-stage (I-II) diagnosis. Systemic therapy improves survival in stage IV patients, yet access to targeted treatments remains limited, particularly among those under the Universal Coverage Scheme (UC). Enhancing treatment accessibility while considering socioeconomic factors and healthcare costs is essential for developing context-appropriate national guidelines.

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Authors Contribution:

NST, ES and TT, planned and designed the conduct of the study. NST, TS, TT, ES, SP, PJ and WS conducted and are responsible for the data analysis. TT, NST and TS wrote and built the final manuscript, and approved the decision to submit the manuscript.

Declaration

Ethics approval and consent to participate

This study was approved by the Ethics Committee, Ramathibodi Hospital, Mahidol University, Thailand, COA. MURA2020/1286.

Conflict of interest.

The authors declare that they have no conflicts of interest.

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