RESEARCH ARTICLE

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Regional Differences in Admissions and Treatment Outcomes for Hepatocellular Carcinoma Patients in Thailand

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Abstract

Background: Hepatocellular carcinoma (HCC) is one of the commonest cancers in Thailand. We report the stage and survival of patients who were admitted under the public universal health fund (NHSO) covering 47 million people to determine if there were regional disparities in the treatment outcomes in the country. **Method:** We used the 2009-2013 Nationwide Hospital Admission Data, Thailand. Patients with hepatocellular carcinoma (HCC) were identified by the ICD10 code C22.0. Procedures were identified by ICD9-CM codes, and deaths were confirmed from the NHSO database and the national citizen registry. Thailand is divided into 6 regions and Bangkok. Hospitals were identified according to their specific reimbursement codes. Survival time started from the day of first admission and was estimated using the Kaplan-Meier method. The statistical method used to compare regions was Chi-squared tests (Pearson, likelihood ratio, linear-by linear association and Mantel-cox). **Results:** There were 36,956 HCC patients admitted during the study period. The overall median survival was 36 days. 1.63% of the patients had surgery, 0.96% had radiofrequency ablation (RFA), and 5.24% had trans-arterial chemoembolization (TACE). 90.24% did not have any tumor-specific therapy. The proportion of patients admitted for tumor-specific therapy vs. no tumor-specific therapy was significantly different between regions in all treatment modalities ($p<0.01$). Each treatment modality showed a wide range of median survival values across the regions ($p<0.01$). The best survival was seen in Bangkok, the South and the North (for surgery, RFA and TACE) and was often more than twice as long as the regions with the lowest survival, Central, East and West. **Conclusions:** There was a large previously-unreported disparity in admissions and outcomes in Thailand for different treatment modalities for HCC. Bangkok and the South had the best treatment outcomes and often had median survivals more than twice as long as those in the West and East. Public policy to reduce this disparity will need to be implemented in the future.

Keywords: Hepatocellular carcinoma- liver neoplasms- hepatectomy- Chemoembolization- survival

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Introduction

Hepatocellular carcinoma (HCC) is a common cause of cancer death worldwide (International Agency for Research on Cancer) and one of the leading causes of cancer deaths in Thailand (Ministry of Public Health, 2015). Traditionally, the high chronic infection rate of Hepatitis B and the high alcohol intake in Thailand have been the main causes for this cancer, but cirrhosis from other causes such as non-alcoholic fatty liver disease (NAFLD), is increasingly seen and may become a major factor in the future.

The treatment of hepatocellular carcinoma is dependent on the stage of the disease, which in turn determines the general outcome of the treatment (European Association for the Study of the Liver.; Heimbach et al., 2018). The disease in the early stages may be curable with surgery or radiofrequency ablation (RFA). The intermediate stage is treated with trans-arterial chemo-embolization (TACE), which can prolong life, but is generally not expected to

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cure (Llovet and Bruix, 2003). Since 2009, patients with metastasis but with preserved liver function may have targeted therapy with sorafenib, a targeted therapy with inhibitory activity against many tyrosine kinases (Llovet et al., 2008).

Other treatments such as radio-embolization and embolization with drug-eluting beads have been introduced to treat non-metastatic HCC, but have not been widely used in Thailand as yet. Transplantation can also be performed but only a small proportion of patients with HCC in Thailand will fulfill the transplant criteria and actually receive donor livers. The majority of patients present in the late stages, at which point the treatment is only palliative.

Many countries have reported poor overall outcomes for HCC and this is particularly noticeable for Asian countries (Norsa'adah and Nurhazalini-Zayani, 2013; Narin et al., 2015; Loho et al., 2016) . One major problem seems to be that symptoms often occur late in the disease when the tumor has grown large or has metastasized. Patients who present at this point frequently have a poor prognosis whatever the treatment they receive.

However, another problem for patients may be the accessibility of the treatment. Some of the treatment modalities outlined above are costly and require expertise. In resource-limited countries, these two factors may limit the availability and accessibility of the treatment for many patients (Maru et al., 2010). Therefore, the outcomes for these patients may be poorer than expected as they do not receive timely standard-of-care treatment. (Faramnuayphol et al., 2008; Aungkulanon et al., 2016).

In Thailand, the medical care for the general population is covered by three public healthcare funds, The Civil Service Health fund, the Social Security Health fund and the National Health Security Office (NHSO), each covering about 5 million, 9.8 Million and 47.5 million people of the population, respectively (Tangcharoensathien et al., 2020). The NHSO is the universal health coverage that covers all the people who are not covered by the other two health care funds and is the largest of the three.

All the healthcare funds in Thailand reimburse the standard treatments for HCC including surgery, RFA and TACE. During the study period sorafenib had not come into general use and currently it is only reimbursable by the Civil Service Health fund and not the NHSO. Transplantation is also only reimbursable by the Civil Service Health fund.

It is likely that the accessibility and availability of these treatments are not uniform across Thailand. Thailand's per capita income varies across the country, both in terms of Gross regional product per capita and the poverty rate (The Office of the National Economic and Social Development Board Thailand), and health provisions in Thailand are often better in major cities compared to the rural areas (The Office of the NESDC). The different regions in Thailand have cities that vary in size and different proportions of people living in the rural areas.

In this study we collaborated with NHSO and analyzed their inpatient data from the years 2009-2013 for patients with HCC. No country-wide HCC data of this size has previously been analyzed for regional treatment outcomes, and we wanted to determine what treatments, costs and outcomes were for HCC across the country.

Methods and Materials

Patients and data

Data for inpatient reimbursement information from the 2009-2013 Nationwide Hospital Admission Data, NHSO, Thailand was used for analysis. The data was obtained for analysis after an agreement between the NHSO and the Gastroenterology Association of Thailand (GAT). This data was collected from the input of doctors and clerks during the admission of patients and it was sent to the NHSO from each hospital for reimbursement for each admission. Matching the same patients who were admitted into different hospitals was performed using individual citizenship numbers. The dataset contained identification and location codes for the hospital the patient was registered with, as well as all hospitals the patient was admitted into in the NHSO system. For our study we used the region of the first hospital that the patient was admitted into with HCC as the patient's region, and we counted any tumor-specific treatment performed during the study period, wherever it was done and during any admission, to indicate that the patient had had a tumor-specific treatment. The ICD10 and ICD9-CM codes were used for reimbursement. We analyzed only patients who were coded for HCC identified by the ICD10 code C22.0. Other possibly related codes, for liver neoplasia unspecified, C22.9, and C22.7, other specified carcinoma of the liver, were tested and found to have different demographic profiles and were not used for analysis. Procedures and operations performed on these patients were identified by ICD9-CM codes, for surgery (ICD9 50.22 partial hepatectomy, 50.3 lobectomy of the liver) local ablation/RFA (ICD950.23 open ablation of liver lesion, 50.24 percutaneous ablation of liver lesion, 50.25 laparoscopic ablation of liver lesion, 50.29 other destruction of liver lesion (e.g. cauterization), 50.94 other injection of therapeutic substance into liver) and Trans-arterial chemoembolization (TACE/TOCE) (ICD9 99.25 injection or infusion of cancer chemotherapeutic substance, chemoembolization/infusion of anti-neoplastic agent). Deaths were confirmed by checking both the NHSO database and the national vital registration database (Ministry of Interior) (Aungkulanon et al., 2016). Basic cleaning of the data was performed by both the NHSO and the study's statistical teams. Comorbidities were found according to the diagnostic coding in ICD10.

Thailand is divided into 6 regions (Northeast, North, Central, South, East, West), and the capital city, Bangkok. The regions vary in size and population as shown in figure 1. The Gross Regional Product (GRP) for the regions in 2011 were (in millions of Baht) NE: 1,114,945; N: 889,914; C: 622,966; S:1,187,420; E:2,016,694; W:402,664; Bangkok and vicinities:4,885,915. Corresponding GRP per capita (in Baht) were NE: 48,549; N: 72,925; C: 204,166; S: 125,270; E: 436,479; W: 108,727; Bangkok and vicinities: 422,141. The Eastern region is the location of many manufacturing industries and the GRP is strongly dominated by manufacturing and mining, (NESDC, 2011) and although it has the highest GRP per capita, the high GRP per capita may not have been representative of the wealth of the majority of people in the Eastern region (Witthayapipopsakul et al., 2019). The locations, size and levels of hospitals were identified according to their specific reimbursement codes.Survival was taken from the day of first admission rather than from time of diagnosis.

The statistical method used to compare regions was Chi-squared tests (Pearson, likelihood ratio, linear-by linear association and Mantel-cox). Median survival was estimated using Kaplan-Meier method and compared using the Log-rank test.

Ethical permission was obtained from the local Ethics review board, Ramathibodi hospital, Mahidol University for the study. Waiver of consent was obtained and patient records/information was anonymized and de-identified prior to analysis.

Results

Admission and costs

In 2009-2013 there were 36,956 patients identified with HCC, who were admitted 67,914 times in 947 hospitals across the country. The results are shown in the Table 1.

The overall cost of admissions for patients with HCC was 1,478,891,525 Baht (approximately 47.7 million US dollars using approximate 2011 exchange rate of 31 Baht/dollar). The highest average cost per admission was for surgery at 94,481 Baht (3048 dollars) and the lowest was for patients who did not receive any tumor-specific therapy, at 18,202 baht (587 dollars) as shown in Table 1.

Overall, of the patients who were admitted with HCC, 1.63% underwent surgery, 0.96% had RFA or other ablative techniques, 5.24% had TACE, and 1.92% had a combination of therapies, whilst the rest (90.24%) did not have any tumor-specific therapy.

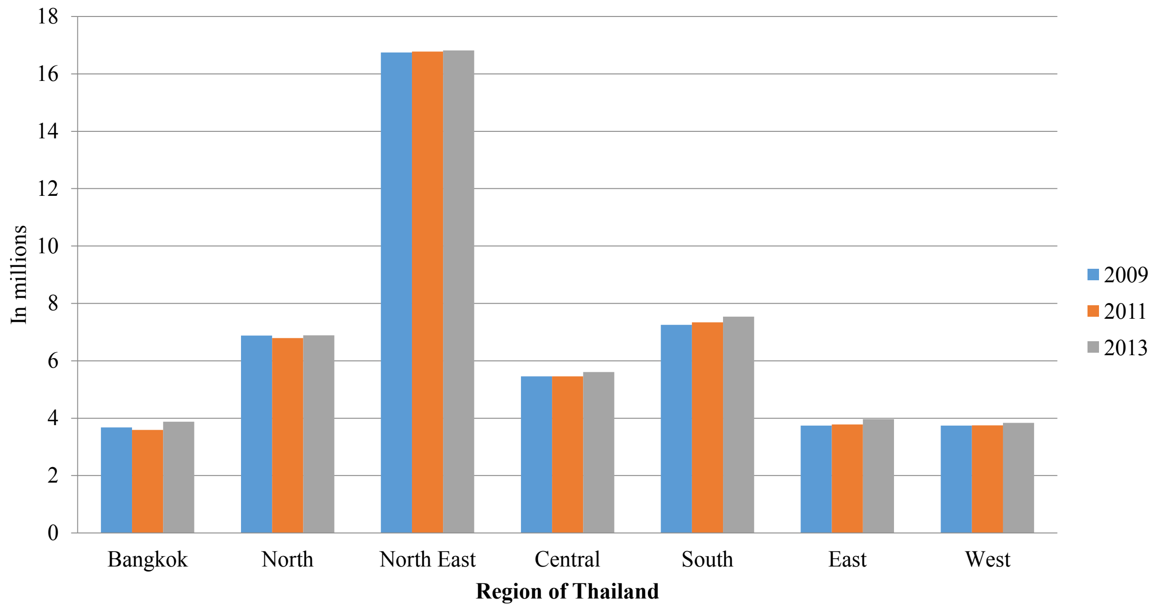

Figure 1. The Population of Thailand Registered with the NHSO, by Region

Table 1. Treatment, Survival and Cost of Admission for Patients with HCC.

	Number of patients (%)	Mean cost per admission (Baht)	Median survival after 1st admission (days)	1-yr survival rate (%)	3-yr survival rate (%)	5-yr survival rate (%)
Overall	36,956 (100)	21779	36	15	5	1
Surgery	603 (1.63)	94481	921	67	24	5
RFA/local ablation	353 (0.96)	39364	887	69	25	3
TACE	1940 (5.25)	35374	296	45	8	2
combination	710 (1.92)	41043	322	46	10	2
No tumor specific treatment	33350 (90.24)	18202	30	11	4	1

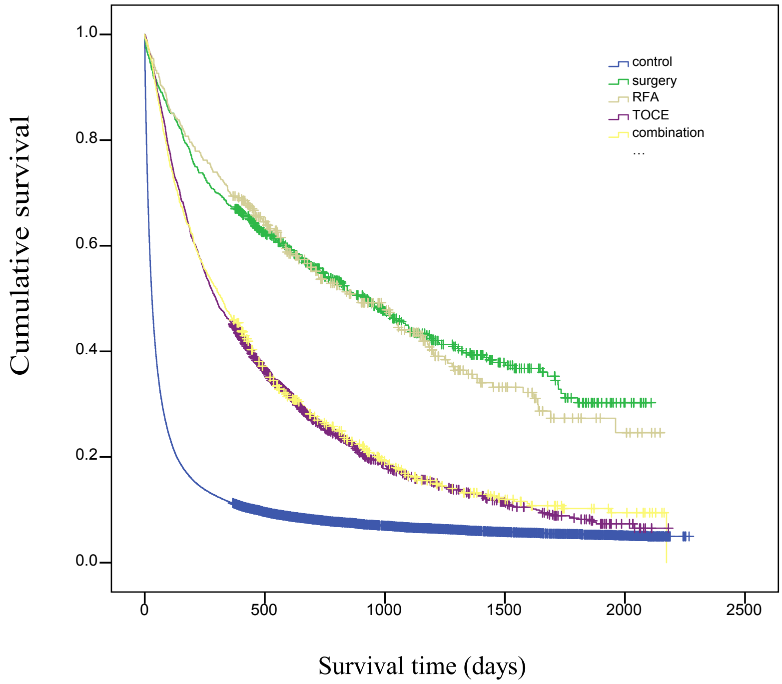

Figure 2. The Survival of HCC Patients in Thailand According to the Treatment Modality

Survival

The overall median survival after first admission was 36 days, and the overall 1, 3, 5-year survival from first admission were 15%, 5% and 1% respectively (Table 1).

The median overall survival after first admission for patients undergoing surgery was 921 days, for patients undergoing RFA: 887 days, TACE: 296 days, and for those not undergoing any tumor-specific therapy the

Table 2. Number of Patients Admitted in Each Region for Each Treatment Modality and the Corresponding Median Survival Time

Region	Surgery	RFA	TACE	Combination treatment	No specific HCC treatment	Total HCC patients admitted 2009-13 (incidence per 100,000 population)
Number of patients admitted						
Bangkok	215	204	974	261	2952	4606 (24.67)
North	109	26	309	31	6213	6688 (19.47)
NE	171	35	129	180	12095	12610 (14.99)
Central	43	12	165	104	4130	4454 (16.12)
South	27	72	210	133	2487	2929 (7.92)
East	25	4	103	1	3061	3194 (16.68)
West	13	0	50	0	2412	2475 (13.06)
Total	603	353	1940	710	33350	36956 (15.23)
P value1	<0.01	<0.01	<0.01	<0.01	<0.01	
Median survival (days)						
Bangkok	1503	1146	371	432	35	101
North	825	589	278	467	29	34
NE	810	329	250	383	29	32
Central	259	234	284	149	31	34
South	1723	845	283	166	34	45
East	220	83	163	---	27	29
West	80	--	140	---	30	31
Total	921	887	296	319	30	36
P value 2	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

The upper half of the table shows the number of patients admitted (2009-2013) for each modality while the lower half of the table shows the corresponding survival (days). P value1 is for the difference in the proportion of patients admitted for the treatment modality for each region (i.e. each region had statistically different percentages for admissions for that treatment modality). P value2 is for the difference in median survival times between regions for each modality (i.e. each region had statistically different median survival times after that treatment modality).

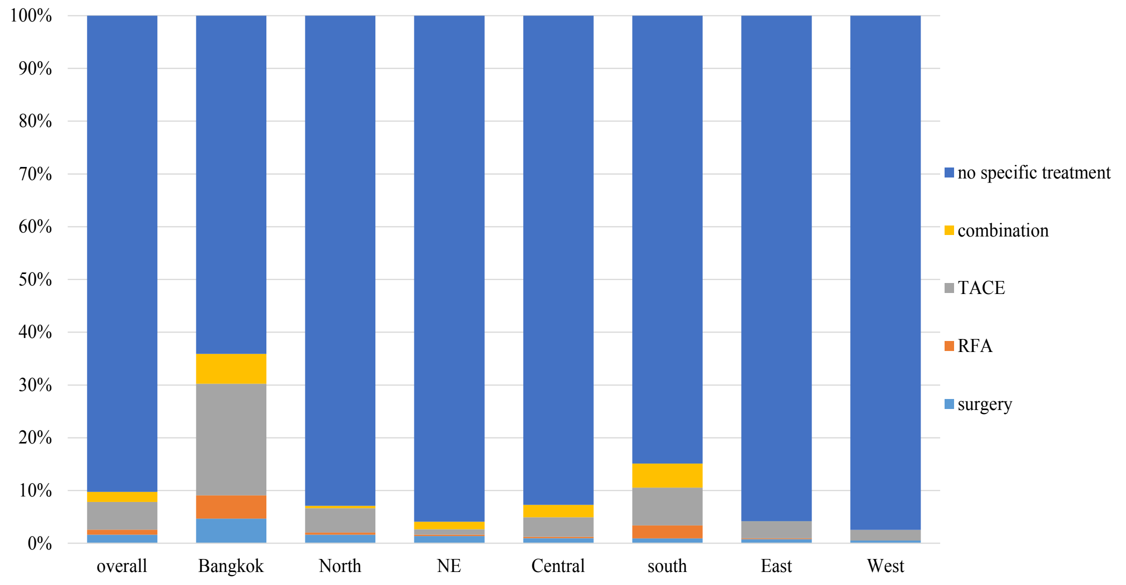

Figure 3. The Proportion of Admitted HCC Patients in Each Region Undergoing Different Treatment Modalities.

median survival was 30 days (p<0.001). One-year survival for surgery and RFA were 67% and 69% respectively with a corresponding 5-year survival rate of 5% and 3%, respectively (Table 1). The comparison survival curves can be seen in Figure 2.

Difference between regions

The incidence of patients admitted for HCC per 100,000 population for each region varied from 7.92 in the South to 24.67 per 100,000 in Bangkok. The proportion of patients admitted for tumor-specific therapy vs. no tumor-specific therapy was found to be significantly different (p<0.01) between regions in all treatment modalities. The region that had the highest proportion of patients admitted for treatment was Bangkok, followed by the South, and the regions with the lowest proportion of patients admitted for treatment were the East and the West (Table 2 and pictured in Figure 3).

For each treatment modality, there was a wide range of median survival values after first admission across the regions (p<0.01). The best survival was seen in Bangkok, the South and the North (for surgery, RFA and TACE) and the survival in this group was often more than twice as long as the regions with the lowest survival, the Central, East and West regions. The median survival after surgery, for example, was 1503, 1723, 825 days for Bangkok, South and North respectively, while it was only 259, 220, 80 days for Central, East and West respectively. This is shown in Table 2 and Figures 5-7.

For patients who did not receive any HCC-specific therapy, the median survival varied between 27 days, in the East, and 35 days in Bangkok. The variation in survival in this group was found to be statistically significant, as shown in Figure 8.

Factors related to outcomes

To find factors associated with the discrepancy in outcomes between regions, patients treated in different regions were compared for differences in age, sex and presence of comorbidities as shown below in Table 3.

Analysis showed that there was a difference between the regions in terms of comorbidities in HCC patients

Table 3. Baseline Characteristics and Reported Comorbidities of Admitted HCC Patients in Different Regions

	S	N	NE	C	W	E	BKK
Age (Median)	58	58	61	60	60	59	59
Sex (% male)	73.6	75.8	70.2	74.6	75.1	73.2	74.3
Cirrhosis (%)	7.9	3.7	2.9	7.1	6.7	7.2	9.2
CAD (%)	0.1	0.2	0.0	0.3	0.5	0.3	1.1
CHF (%)	1.5	0.9	0.8	1.4	2.3	1.4	1.4
CKD (%)	0.6	0.7	1.0	0.3	0.5	0.8	1.1
COPD (%)	1.1	1.7	0.7	1.0	1.9	1.1	0.9
CVA (%)	0.1	0.1	0.2	0.0	0.0	0.2	0.1
Sepsis (%)	4.3	5.4	5.8	5.7	5.2	6.0	5.5
DM (%)	10.7	8.0	10.6	10.2	10.7	12.1	17.6
GIB (%)	7.8	7.5	5.9	7.4	7.7	8.0	6.0

CAD, coronary artery disease; CHF, chronic heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, diabetes mellitus; GIB, gastrointestinal bleeding

Table 4. Univariate Analysis for Factors Related to Survival of Patients with HCC.

	Hazard ratio	95% CI	P value
Age (as continuous variable)	1.007	1.006-1.007	<0.001
Sex (reference: male)	0.88	0.859-0.902	<0.001
comorbidities			
DM	0.849	0.820-0.878	<0.001
GIB	1.363	1.307-1.421	<0.001
Sepsis	1.762	1.682-1.845	<0.001
Stroke	1.113	0.819-1.512	0.494
COPD	0.989	0.892-1.097	0.831
CKD	1.14	1.010-1.303	0.034
CHF	1.182	1.072-1.303	0.001
CAD	0.725	0.591-0.888	0.002
Cirrhosis	0.928	0.885-0.973	0.002
Region of admission			
South	1	-	-
North	1.159	1.123-1.197	<0.001
Northeast	1.23	1.193-1.268	<0.001
Central	1.221	1.179-1.265	<0.001
West	1.341	1.288-1.396	<0.001
East	1.351	1.301-1.402	<0.001
Bangkok	0.701	0.678-0.724	<0.001
Treatment modality			
No tumor-specific treatment	1	-	-
Surgery	0.221	0.202-0.243	<0.001
RFA	0.259	0.239-0.281	<0.001
TACE/TOCE	0.38	0.369-0.391	<0.001
Combination	0.37	0.354-0.388	<0.001

CAD, coronary artery disease; CHF, chronic heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, diabetes mellitus; GIB, gastrointestinal bleeding; RFA, radiofrequency ablation; TACE/TOCE, transarterial/ transarterial oily chemoembolization

who were admitted. HCC patients had different levels of documented cirrhosis, coronary artery disease, chronic heart failure, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, and gastrointestinal bleeding ($p<0.001$) but not in cerebrovascular accidents and sepsis reported.

Univariate and multivariate regression analyses were performed to find any association between these factors and the survival of the patients, as shown in Tables 4 and 5 respectively.

Multivariate analysis showed that treatment modality was the most important factor associated survival after admission for HCC. The hazard ratio was 0.246 (0.22-0.27 95%CI) for surgical treatment, 0.30 (0.27-0.33 95%CI) for ablation therapy/RFA and 0.427 (0.41-0.44 95%CI) for TACE compared to not receiving any tumor-specific treatment. The hazard ratio for combination therapy was 0.405 (0.39-0.46 95% CI). Other factors found to be independently related to survival included age, sex, comorbidities (diabetes, gastrointestinal bleeding, chronic liver disease, sepsis and cirrhosis) and the region where the admission took place.

Table 5. Multivariate Logistic Regression Analysis for Factors Related to Survival in Admitted Patients with HCC.

	Hazard ratio	95% CI	P value
Age (per increasing year)	1.003	1.003-1.004	<0.001
Sex (reference: male)	0.858	0.842-0.874	<0.001
comorbidities			
DM	0.861	0.840-0.883	<0.001
GIB	1.197	1.162-1.234	<0.001
Sepsis	1.59	1.534-1.647	<0.001
Stroke	0.897	0.695-1.157	0.402
COPD	0.93	0.859-1.006	0.071
CKD	1.106	1.013-1.209	0.025
CHF	1.024	0.949-1.105	0.542
CAD	0.86	0.747-0.991	0.037
Cirrhosis	0.929	0.896-0.963	<0.001
Region of admission			
South	1		-
North	1.042	1.009-1.076	0.012
Northeast	1.071	1.039-1.105	<0.001
Central	1.081	1.044-1.120	<0.001
West	1.101	1.058-1.147	<0.001
East	1.166	1.123-1.211	<0.001
Bangkok	0.876	0.843-0.902	<0.001
Treatment modality			
No tumor-specific treatment	1		-
Surgery	0.246	0.224-0.270	<0.001
RFA	0.3	0.277-0.326	<0.001
TOCE	0.427	0.413-0.440	<0.001
Combination	0.405	0.387-0.425	<0.001

CAD, coronary artery disease; CHF, chronic heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, diabetes mellitus; GIB, gastrointestinal bleeding; RFA, radiofrequency ablation; TACE/TOCE, transarterial/ transarterial oily chemoembolization

Discussion

This is the first nationwide study looking at the regional outcomes of treatment of HCC in Thailand. The NHSO, whose data was used in this study, covered approximately 47 out of 60 million people in Thailand. The results confirmed that HCC is a common disease in Thailand, and that only a very small percentage (9.76%) of patients received curative or tumor-specific treatment. In addition, there were marked variations in outcomes for survival after treatment depending on the region of the country.

The NHSO is the largest public healthcare funder, and is financially supported by the government. People are required to register locally to be eligible for subsidized healthcare coverage. It is different from the other two

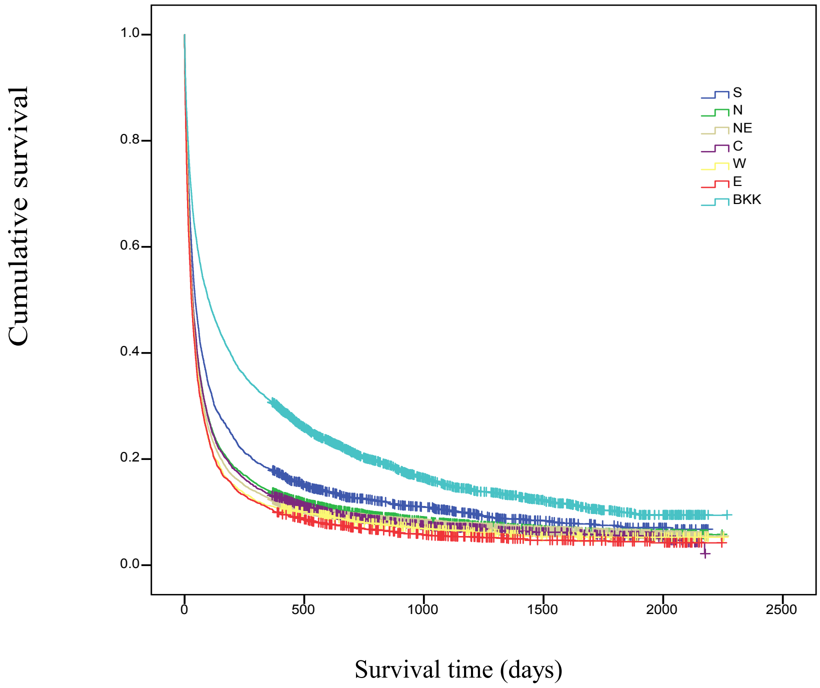

Figure 4. The Overall Survival of Patients with HCC Admitted in Each Region.

healthcare funds in being the most universal healthcare fund, and patients have a wider age range as well as wider income status compared to the other two healthcare funds. Subsidization for the NHSO has been financially more limited than the Civil Service healthcare fund but it does include cost of surgery, RFA or TACE, whereas sorafenib is not (and as it does not require admission is not represented in the data). The NHSO requires certain inpatient data from the hospitals to obtain reimbursement for the cost of admission and treatment, and this was the data used in this study. Such data include the demographics of the patients as well as the disease, comorbidities and the treatment used. Data concerning death in our study was taken from 2 reliable sources, the NHSO and the national death registry.

The incidence of patients with HCC who were admitted varied from 7.92 to 24.67/100,000 population depending on the region. This was within the range of 18.2 /100,000 population estimated for Southeast Asia by the GLOBOCAN database analysis (Venook et al., 2010).

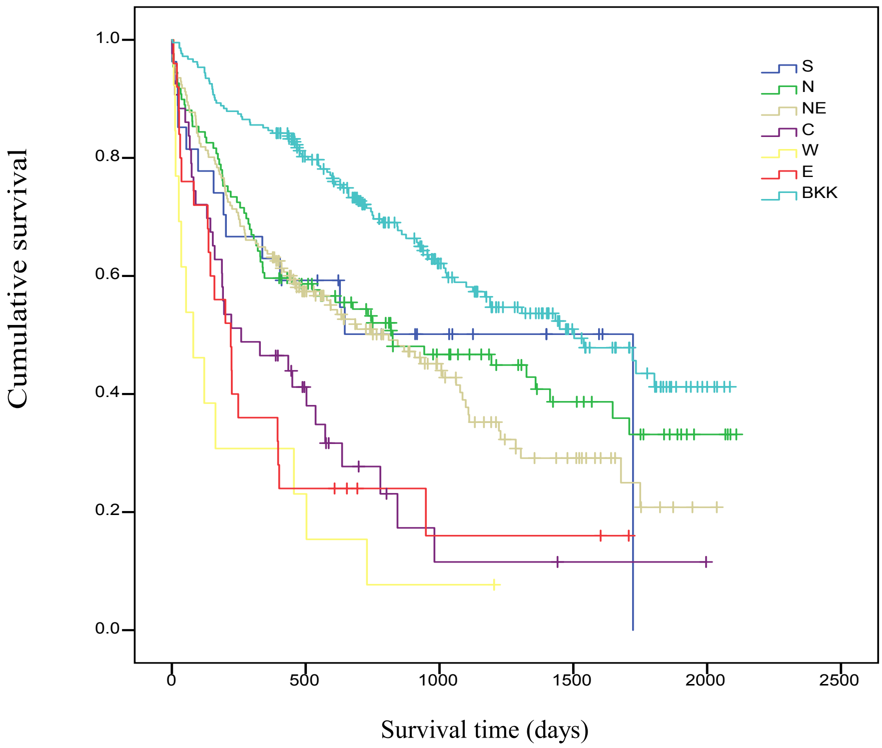

Figure 5. Survival Curve for Patients Undergoing Surgery for HCC in Different Regions in Thailand.

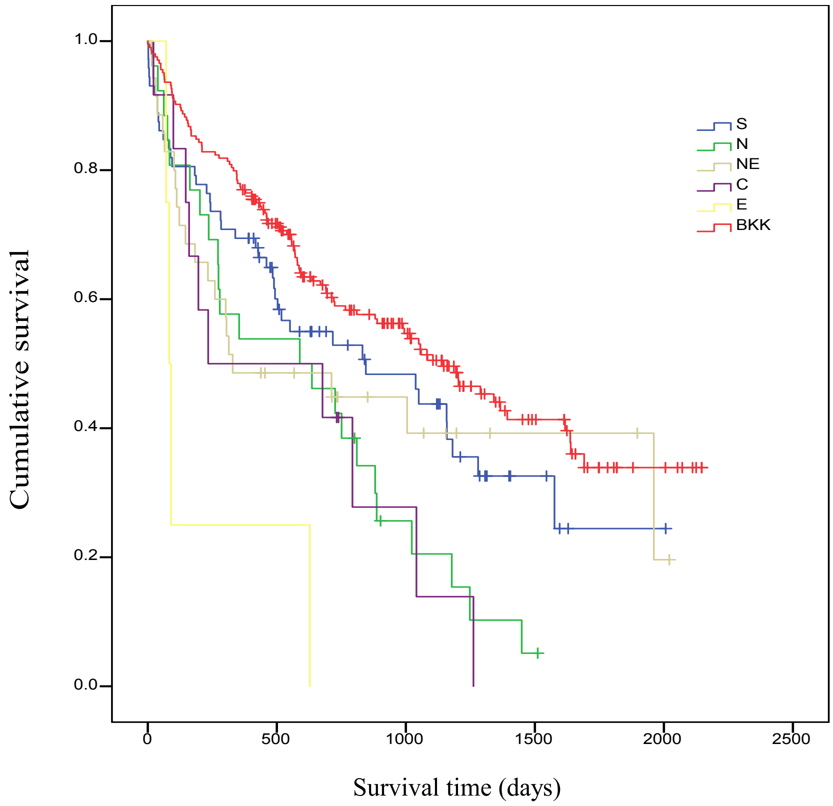

Figure 6. Survival Curve for Patients Undergoing RFA in Different Regions of Thailand.

Our incidence rate is more than Singapore (7.1/100,000 population) but less than many of the East Asian countries such as Korea, Japan, China, Taiwan (Zhu et al., 2016).

The total cost of treatment was calculated to be 1,478,891,525 Baht for the 5 years of the study. The average cost per admission was highest for surgery, at 94,481 Baht, although the total number of admissions was the lowest (n=603), whereas the reverse was found for patients who were admitted but did not have any tumor specific treatment. In the latter case the average cost was the least among the treatment modalities, at 18,303 baht, but there were 33,350 patients in total in this group. This

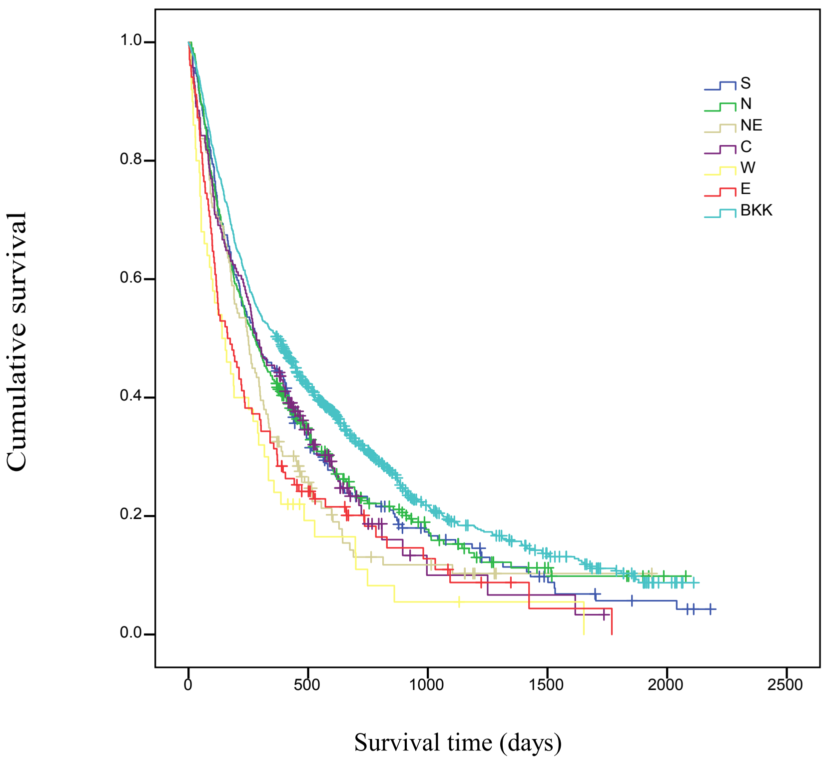

Figure 7. Survival Curve for Patients Undergoing TACE in Different Regions in Thailand

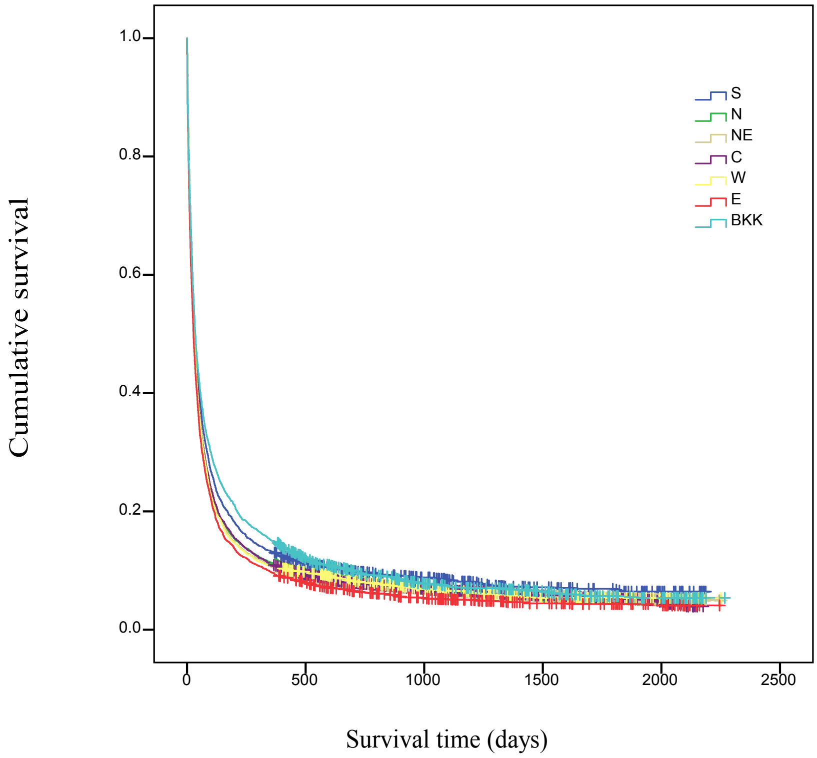

Figure 8. Survival Curve for Patients who did not Receive HCC-specific Treatment

compares with the estimated annual cost of $34.8million, and $35.7million for surgery and TACE for HCC in USA. The overall cost per-patient in USA was $32,907 (Lang et al., 2009) compared to our average cost per admission of 21,779 Baht.

In Thailand patients are admitted for surgery, RFA and TACE. The results show that there was a low percentage of patients who underwent these curative and tumor-specific treatments. Only 2.6% of patients received potentially curative treatments such as surgery and local ablation, while only 9.76% of patients admitted for HCC under the NHSO had any tumor-specific therapy (and conversely this meant that approximately 90% did not receive any tumor-specific therapy). Although this concerning percentage may be slightly inaccurate due to the natural errors of hospital coding and some patients may have had procedures done at private hospitals, we believe the general magnitude of the figure is correct for patients covered by the NHSO for a number of reasons.

Firstly, the data and percentage represent only those patients covered by the NHSO. Since 2004, personal identification codes and the membership database have been synchronized between all three healthcare funds allowing tracking of individuals across all healthcare schemes (Sakunphanit, 2008). By law the coverage of each scheme is mutually exclusive, and except for people who lose their social security funding because of loss of work, this means that patients would not have any procedures done under another healthcare scheme. One limitation of our data would be that patients who were admitted using private health insurance at private hospitals would not have been coded under the NHSO and this may be one source of error in the percentage reported in this study. However, we think the effect of this error would be low. To be miscounted as HCC without tumor-specific treatment under the NHSO despite having private treatment, the patient would have to convert back to care under the universal healthcare scheme (NHSO) after tumor-specific treatment. Although we cannot rule this out, there would be little reason for patients to change their reimbursement scheme from private insurance to NHSO just for palliation at the end of their lives. In any case, most of the patients covered by the NHSO included the poorest segments of society, with the poorest and next poorest quintiles of the Thai population accounting for more than half (60%) of those covered by NHSO, while 7% of the patients are in the richest quintile of the population (compared to the Social service Healthcare scheme and Civil Service Healthcare scheme of whom 39% and 47% of members are in the richest quintiles respectively) (Sakunphanit, 2008). The NHSO also covered most of the poor Thai rural population (Limwattananon et al., 2012). People who work in the formal sector of business are covered by the Social Security healthcare fund and are mutually excluded from the NHSO, in contrast, patients in the NHSO often work in the informal sector, are self-employed in small businesses, agriculture or are unemployed. These patients rarely have private insurance in Thailand and the NHSO was formed to some extent to reduce the risk of catastrophic financial loss from illness in this group (Tangcharoensathien et al., 2020). We therefore think that this source of error (the intermittent use of private insurance) would have had a minimal impact on the general magnitude of the percentage of NHSO patients receiving, and not receiving, tumor-specific therapy.

Other possible sources of error, such as repeat hospitalizations were also clearly documented in the dataset using identifier codes and were accounted for in the analysis. Prior admissions for tumor-specific treatment before coding for HCC (C22.0), such as the scenario of having a hepatectomy without coding for HCC, would have been included in the analysis if it was within the time frame of the dataset. We think that the frequency of this occurrence would have been low and the dataset duration, being 5 years, would have been long enough to cover this period for the majority of patients.

It is important to note that this low percentage of patients receiving tumor-specific treatment in this study represented only patients covered by the NHSO. Patients in other healthcare schemes may have had higher rates of treatment. Unpublished analysis from a previously reported dataset (Poovorawan et al., 2015) (access permitted by the Gastroenterology Association of Thailand), for admissions for HCC for all 3 healthcare funds in 2010 showed that the percentage of admissions for HCC for specific treatments (surgery/ ablation/ TACE) were higher in the other healthcare schemes, at 48.9%, 32.1%, vs 20.3% of all HCC admissions for Civil Service Healthcare fund, Social Security fund, and NHSO respectively. Unfortunately, this dataset did not allow for identification of patients who had repeated hospitalizations or for survival and so was not published. However, these results suggest that a larger proportion of admissions for treatment was seen in the other healthcare funds compared to the NHSO.

Secondly, although it is possible that a certain proportion of patients did not undergo these treatments due to their age, other comorbidities or their underlying liver disease, a more common reason for the low tumor-specific treatment number is the late stage of HCC at diagnosis. Many studies have reported the fact that HCC is often detected at a late stage in Thailand. Even studies from tertiary referral hospitals whose patients are enriched with referred patients for surgery/ablation and TACE, including patients from all healthcare schemes, and where ultrasound screening is available, show that a large proportion of patients are still diagnosed in the late stages. A study from a tertiary center in the North of Thailand reported only 13.9% of patients were in BCLC stage A, 36.6% stage B, 33.1% and 15.0% for stages C and D respectively (Leerapun et al., 2013). Similarly, an earlier study tertiary referral center in the south reported that 15% of their patients in Okuda stage 1, 61% in stage 2, and 24% in stage 3, but 80% of their patients had cirrhosis with Child-Pugh class B or C, and 50% had portal vein thrombosis. For the percentage receiving treatment, only 0.3% of the patients had ablation therapy, 1.2% had hepatectomy, 13.1% had TACE, and 3.6% had combination therapy (Sithinamsuwan et al., 2000). Patients who were unfit for treatment would not have been referred for treatment in these tertiary centers in the first place (Chaiteerakij et al., 2017) and a number of patients diagnosed in these centers even refused treatment based on their cultural beliefs (Leerapun et al., 2013). A study from a tertiary referral center in the central region of Thailand reported that 75.4% of patients were found in the intermediate or late stages of disease (Somboon et al., 2014) and an Indian study from a tertiary hospital reported 83.5% of their HCC patients presenting with features of decompensated cirrhosis (Sood et al., 2014). In terms of the proportion of patients receiving tumor-specific treatment, the low rate of curative and non-curative tumor-specific treatment in our population is not unique. A Cambodian study from a tertiary center reported 84% of their HCC patients had palliative treatment, 13.9% had systemic or oral chemotherapy and only 2.1% had hepatectomy as treatment (Chassagne et al., 2016). Even in the developed countries, such as USA and France, the level of tumor-specific treatment is not as high as one would expect, with surgery reported in the Medicare system in 8.2% of HCC patients in the USA and 11.2% for France; ablation was used in 4.1% and 7.8%, and TACE was used in 4% and 12% respectively (El-Serag et al., 2006; Goutte et al., 2017). Although these rates were higher than ours, it is sad that the rate of curative treatment was at best still below 20%, and the Medicare rate for the combined percentage of patients who had ablation/ surgery/ TACE was only 16.2%.

Thirdly, one other major factor that needs to be considered is that the number receiving treatment may have been limited due to difficulties in accessing healthcare in some parts of the country. This may have been partly due to the patients' poor economic status, as described above, but also due to the lack of ultrasound screening and other specialty services outside urban areas. In addition to the fact that NHSO is the healthcare scheme that covered the poorest citizens in Thailand, and that there was a large difference in the Gross Regional Production (GRP) between regions and GRP per capita as described earlier, there was also a big difference in the health workforce expenditure per capita across provinces, although this was improving by 2012. (Ruangratanatrai et al., 2015)

Although successive Thai governments have worked hard to reduce the inequalities in healthcare access in the rural areas over many decades, the focus has mainly been on primary care (Kitreerawutiwong et al., 2017). This has resulted in the development of multiple small district hospitals to cover the rural population and strategies to encourage primary care physicians and doctors to work in rural areas. (Kitreerawutiwong et al., 2017). However, due the lack of doctors in the rural areas, only 20% of the primary care OPD services are staffed by doctors whilst the rest are serviced by nurses and health officers (Kitreerawutiwong et al., 2017; Pagaiya et al., 2019). One of the strategies to increase the doctor: patient ratio was the compulsory rural service for new medical graduates (Kitreerawutiwong et al., 2017) but these new graduates would not have been able to perform complete ultrasound abdominal examinations let alone other specialist procedures related to HCC treatment. Unfortunately, ultrasound examinations in Thailand are performed only by doctors and only recently has the first sonographer school been opened (Siripongsakun, 2020). This would mean that for the majority of patients who did not live in major urban areas, ultrasound screening for HCC would not have been easily available, and the Thai Association for the Study of the Liver (THASL) has recognized this lack of ultrasound capacity by extending the recommended ultrasound surveillance interval from 6 to 12 months in the management guidelines for Hepatocellular carcinoma (THASL, 2016). A study from one of the largest tertiary referral centers in Bangkok showed that despite their selective patient population and the availability of local ultrasound surveillance, only 23% of their HCC's were diagnosed by surveillance, even when surveillance was loosely defined as having one ultrasound within 1 year of diagnosis (Chaiteerakij et al., 2017).

If patients wanted to have ultrasound surveillance, many would have had to travel to a provincial or regional center. They would have had to pay their own travel expenses, as this is not covered by the NHSO, as well as lose time and income for traveling. A recent study reported that the patient's income level was a significant factor in adherence to HCC surveillance, and a monthly income of more than 10,000 Baht was a significant factor for adherence (OR 4.6, 95%CI 1.37-15.21) (Rattanasupar et al., 2021). Unfortunately, another study found that 50-90% of patients covered by NHSO at sub-district rural hospitals had incomes less than 7,500 Baht per month (Kitreerawutiwong et al., 2017). So it would seem that ultrasound surveillance, an important tool for the early detection of HCC, may not have been easily accessible in many areas, and patients covered by the NHSO may have been less likely to adhere to surveillance for economic reasons.

With the late detection of HCC, for the reasons described above, the treatment of choice for many would have been TACE. However, this treatment is performed in tertiary referral centers by interventional radiology specialists. The public health policy focus on primary care by previous governments has meant that this service is not available in every province. A recent survey by the Royal College of Radiologist (Thailand) and the Association of Interventional Radiologist Thailand (unpublished, personal communication), has shown that there were 87 interventional radiologists in Thailand in 2020 (and much less in 2009-2013), and 57% of these interventional radiologists worked in Bangkok, 16% in the South, 12% in the North, 7% in the North-East, 5% in the Central area, and 3% in the East. There were only 25 hospitals outside of Bangkok that had the capacity to perform TACE in 2020. Capacity for TACE during 2000-2010 was even less with 11 hospitals performing TACE in the country (unpublished data from the Association of Interventional Radiologist Thailand). Outside of Bangkok, there were 2 hospitals in the North, 4 hospitals in the North-East, 3 hospitals in the Central area, 1 in the East, 1 in the South and none in the West that could perform TACE during 2000-2010. This meant that patients and their relatives in 50-60 provinces would have had to travel to tertiary centers in other provinces for TACE. If we look at the proportion of patients admitted for tumor-specific treatments in each region, which for Bangkok was 35.9%, South 15.1%, Central 7.3%, North 7.1%, North-East 4.1%, East 4.2%, West 2.5%, we can see that in well-resourced areas, such as Bangkok, the percentage of patients who had treatment was actually very high. The South which had the second highest number of interventional radiologists also had the second highest proportion of patients who had tumor-specific treatments. Other regions with low numbers of interventional radiologists also had lower proportions of patients who had tumor-specific treatments. This trend would seem to point to the lack of specialist treatment capacity outside of major urban areas as a significant factor for the low percentage of patients receiving tumor-specific treatment.

The overall mortality for these admitted patients was rather poor, with the overall 1-year survival after first admission of 15% and 5-year survival of 1%. The median survival after admission was only 36 days. Our results are worse than that reported in a similar study from France where the median survival after admission was 9.4 months (Goutte et al., 2017), but similar to an earlier study in Thailand where the overall survival was 2.1 months (Sithinamsuwan et al., 2000). The lower overall survival is due to the larger proportion of patients admitted for palliative treatment and end-of-life care compared to the French study. These patients who did not have any tumor-specific therapy had a median survival of 30 days after admission.

For patients undergoing tumor specific treatment such as surgery, RFA or TACE the one-year survival was better, at 67%, 69% and 49% respectively. This is consistent with some other studies. But when the 3-year and 5-year survival data for each treatment modality is examined, our data shows that our survival data is inferior to many other reported studies.

Our survival after surgery (67%, 24%, 5% for 1-year, 3-year and 5-year survival, respectively) is consistent with the 1992-3 SEER Medicare dataset where they reported a 1-yr survival after surgical resection of 61.7% and a 3-year survival 30.9% (El-Serag et al., 2006). However, it compares unfavorably to other large databases reported, such as the one from Taiwan reporting 23,107 major hepatectomies from 1998-2009. The 1-year, 3-year and 5-year survival after hepatectomy in the Taiwan study were 83%, 67% and 53% respectively (Lu et al., 2014).

For Ablation therapy, the 1-yr and 3-yr survival in the Medicare system was reported to be 59.8% and 9.8% (El-Serag et al., 2006). This compares to our data which showed that the 1 and 3-year survival after ablation was 69% and 25%. A systematic review and meta-analysis done on patients undergoing RFA reported that the overall survival after treatment in randomized controlled or comparative trials, in comparison to unselected patients, varied between 96-100% for 1-year survival, 52-92% for 3-year survival and 41-77% for 5 year-survival (Tiong and Maddern, 2011).

Our data showed that the survival in Thailand in the NHSO system, after TACE was 45%, 8% and 2% for the 1-,3- and 5-year survival, respectively. In the Medicare study the TACE the 1-year survival was 44.3% and 3-yr survival was 6.1%, which was approximately the same (El-Serag et al., 2006). A smaller study from Barcelona demonstrated 1- and 3-year survival rates of 61% and 19% (Llado et al., 2000). Many other studies have reported only 1- and 2-year survival rates, these varied between 51-82% and 18-63% respectively (Llovet and Bruix, 2003; Brown et al., 2004).

For patients who were admitted and who had no tumor-specific treatment, the survival after first admission was extremely poor. The median survival was 30 days after first admission and only 11% were alive after 1 year. Unfortunately, there is no formal hospice system in Thailand, and many patients come to the hospital to be treated during their final days. They would have received symptom-based palliative treatment under the NHSO. The number reported in this study may have been an underestimate because in some parts of the country, it is the local culture for the relatives to take the patient back home to be cared for and to die when death is deemed unavoidable and imminent (Leerapun et al., 2013). These patients may therefore not have been registered as an inpatient if the diagnosis and dire prognosis was given in the outpatient clinic if it was detected there in the terminal stage. Previous studies have reported very short survival after diagnosis (in comparison to survival after first admission used in our study) in patients who did not qualify for any tumor-specific treatments, from 1.6 months (Sithinamsuwan et al., 2000), 2.3 months (Pawarode et al., 2000), to 4 months (Somboon et al., 2014).

Another important point about survival was that there were large differences between the regions for the survival time after treatment. Analysis of the survival outcomes after admission for tumor-specific treatment revealed large discrepancies between each region. The differences can be seen in both the overall survival and the survival for each treatment modality. The regional ranking for the survival outcomes also seemed to show a pattern that was generally unchanged whichever treatment modality was used.

The striking thing was that the median survival across the regions could be vastly different, the median survival in Bangkok sometimes being more than twice as long as some other regions. For example, for surgery, Bangkok had a median survival of 1,503 days whereas the central region had a median survival of 259 days and the East had a median survival of only 220 days after surgery. A similar difference could be seen in patients undergoing RFA and TACE. This difference in survival persisted even when other risk factors were taken into account, as shown in our multivariate analysis (Table 5). The overall ranking in terms of the best to the worst regions for survival after treatment was Bangkok, the South, the North, Northeast, Central region, the West and lastly the East. It is not clear from the current data whether the difference in outcomes was related to the availability of treatment, patient selection, or other patient factors such as education or household income (Shen et al., 2017). Unfortunately, the NHSO did not collect these data. However, data from the Office of the National Economic and Social Development board showed that there were significant differences in the income per household, gross regional product per capita and poverty rates between many regions and Bangkok (The Office of the National Economic and Social Development Board Thailand), the so-called 'Urban-rural gap'. Another possibility may be the number of large tertiary hospitals in the region. Large tertiary hospitals performing large volume surgery have been reported to have better outcomes for HCC treatments, whether for surgery or other therapies (Glasgow et al., 1999; Mokdad et al., 2016). All of the above factors will need to be investigated in future studies.

One other possibility includes the fact that many patients are referred to the tertiary hospitals in Bangkok for treatment. It may be that patients with better prognosis were referred or were accepted for treatments in Bangkok, while those with worse prognosis remained and were treated locally, producing a lower survival rate in regions outside Bangkok. However, we do not have the clinical information of the patients in the database to compare and test this hypothesis.

The reported comorbidities also varied between the regions. Most notable were the differences between Bangkok and the provinces. Bangkok had higher reported levels of cirrhosis, coronary artery disease, diabetes and kidney disease, but a lower level of gastrointestinal bleeding. The Western region seemed to have the highest levels of heart failure and chronic pulmonary disease. When these were analyzed along with other factors, sepsis was found to be independently associated most with worsening survival, while diabetes, coronary artery disease and cirrhosis were surprisingly found to factors associated with better survival in patients with HCC. It seems hard to believe that these diseases in themselves offer a protection to patients with HCC, and it is more likely that they may be confounding factors. One possibility is that these patients are under constant medical review and therefore their HCCs are detected at an earlier stage and have a better prognosis.

Other possibilities may include the fact that patients with diabetes have non-alcoholic liver disease which does not progress as rapidly as viral hepatitis. However, in opposition to this idea, other studies have suggested that diabetes worsen the survival of patients with HCC (Wang et al., 2014; Su et al., 2017).

Patients with coronary artery disease, but not patients with heart failure also seemed to have better outcomes. There is some evidence that HMG-CoA reductase inhibitors, which are commonly prescribed for patients with ischemic heart disease, improves survival of HCC patients (Kawata et al., 2001; Graf et al., 2008).

For patients reported to have cirrhosis, it would be odd that these patients should have had better outcomes than those without cirrhosis. A more probable reason would be that the better outcome was a result of early detection and biased reporting. Patients who were reported as having cirrhosis may have been under more specialist care, with more intense monitoring and treatment, and therefore associated with earlier detection and better outcomes. Also, patients who presented with end stage massive infiltration of the liver probably may not have been investigated to see if cirrhosis was present or not, making the reporting of cirrhosis less likely in those with poorer prognosis. In any case there seemed to be evidence for selective reporting of cirrhosis in our study as there were only 3-9.5% of patients reported with cirrhosis, while the expected rates of cirrhosis would be around 50-60% at the very least (Colombo et al., 1991; Cauble et al., 2013).

Other factors which were found to be associated with survival include age, sex and the treatment modality. Older patients had worse survival. Female patients were found to have better survival. In a US study, women were more likely to present with compensated liver disease and receive hepatic resection for their HCC compared to men (Cauble et al., 2013). They also had better inpatient mortality compared to men. Unfortunately, we did not investigate this aspect of the data further in our study.

Unsurprisingly the treatment modality was the most important factor in determining survival, with patients undergoing surgery having the best outcomes and those with TACE treatment the worst. As the choice of treatment depended on the stage at diagnosis, the importance of early detection to improve outcomes could not be more emphasized.

There were some limitations to this study. Firstly, the data did not include clinical details such as the date of diagnosis nor the stage of the disease. Secondly, inherent to these types of database, there could have been coding errors in the diagnostic reporting and in the omission of comorbidities (Goutte et al., 2017). However, we have tried to focus on the more solid end-points in our analysis, including treatment modality, date of treatment and date of death, which for the latter was confirmed by two sources. Another issue with the coding was that no separate coding was found for TACE and the systemic infusion of chemotherapy, making it difficult to distinguish the two treatments. As the common practice was to give and reimburse TACE and no chemotherapeutic agent has been recommended or reimbursed by the NHSO for HCC, we assumed that the coding was for TACE. Lastly, this dataset did not include treatment performed in private hospitals, and some patients covered by the NHSO could potentially have had part of their treatment in the private sector before returning for treatment under the NHSO, distorting our analysis. However, we did not think that this occurred frequently for the explanations described above.

In summary this study shows that HCC is common in Thailand and that only a small proportion (9.76%) of patients with HCC were admitted for treatment of the tumor in the universal health coverage scheme. The majority seemed to have been admitted for symptomatic and palliative treatment. Overall, these patients had a median survival of about 36 days after their first admission. There also appeared to be a large discrepancy between the outcomes of surgery, RFA and TACE between different regions in the country, with the ranking pattern showing that Bangkok had the best outcomes then the South, North, Northeast, Central area, the West and lastly the East. Further studies to investigate the causes of this discrepancy is needed after which public policy to reduce this disparity should be implemented.

Author Contribution Statement

Taya Kitiyakara: Conceptualization, Methodology, Writing original draft, review & editing, Validation, Apinya Leerapun: Writing - review & editing, Chinnavat Sutthivanan: Writing - review & editing, Kittiyod Poovorawan: Investigation, Writing - review & editing, Validation, Wirichada Pan-Ngum: Data curation, investigation, Formal analysis and Visualization, Ngamphol Soonthornworasiri: Data curation, investigation and Formal analysis, Roongruedee Chaiteerakij: Writing - review & editing, Sombat Treeprasertsuk: Supervision, Writing - review & editing, Validation, Kamthorn Phaoswasdi: Project administration, resources, Pisaln Mairiang: Project administration, resources, obtained data for analysis, Chomsri Kositchaiwat: Project administration, resources, obtained data for analysis. All authors read and approved the final manuscript.

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Study approval

The study was approved by the Gastroenterology Association of Thailand in collaboration with the NHSO, as part of program to analyze the NHSO database for gastroenterological and hepatic diseases.

Ethical approval

The study was approved by The Committee on Human Rights related to Research involving Human subjects, Faculty of Medicine, Ramathibodi Hospital, Mahidol University (protocol number ID11-60-85).

Availability of data

All available raw data will not be shared as it contained confidential patient information that abide by the signed contract and regulations.

List of abbreviations

HCC: hepatocellular carcinoma
ICD10: International classification of diseases 10
ICD9-CM
TACE/TOCE: trans-arterial chemoembolization/transarterial-oily chemoembolization
RFA: radiofrequency ablation
NAFLD: Non-alcoholic fatty liver disease
NHSO: National Health Security Office
GAT: Gastroenterology Association of Thailand
S/N/NE/C/W/E: South/North/Northeast/Central/West/East provinces of Thailand
BKK: Bangkok
CAD: Coronary artery disease
CHF: Chronic Heart failure
CKD: Chronic kidney disease
COPD: Chronic obstructive pulmonary disease
CVA: Cerebro-vascular accident
DM: Diabetes Mellitus
GIB: gastrointestinal bleeding

Conflicts of interest

The authors declare that they do not have any conflict of interest.

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