RESEARCH ARTICLE

Investigating Up-to-Seven Criteria and APRI (AST Platelet Ratio) as Prognostic Factors in Intermediate-Stage Hepatocellular Carcinoma Patients Who Received Transarterial Chemoembolization

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Abstract

Background: Transarterial chemoembolization (TACE) is one of the locoregional treatments for intermediate-stage hepatocellular carcinoma (HCC). Multidetector computed tomography (MDCT) is a widely used diagnostic tool for HCC. It can also evaluate tumor size, tumor number, and tumor invasion. This study aimed to determine the median survival time in intermediate-stage HCC patients who underwent TACE and to find out prognostic factors influencing patients' survival time after TACE. **Methods:** A computerized search of medical record database in Maharaj Nakorn ChiangMai Hospital from January 2016 to December 2019 revealed 187 intermediate-stage HCC patients who received TACE as the first-line treatment. **Results:** The median survival time of patients in this study was 9.9 months (95% CI: 8.3-11.6). The patients with aspartate aminotransferase-to-platelet ratio (APRI) less than 0.5 had a significantly better median survival time as compared with patients with APRI ratio more than 0.5; (13.2 months versus 9.9 months, p-value < 0.05). Univariate and multivariate Cox regression analysis demonstrated that tumor number > 7 and tumor size > 5 centimeters (cm) could be considered as independent parameters predicting poor overall survival time in the sufferers (HR 2.64 95%CI 1.68-4.15 and HR 2.38 95%CI 1.32-4.31, respectively). **Conclusion:** Based on our findings, patients with intermediate-stage HCC who received TACE had a lower median survival time compared to previous studies. However, we identified APRI less than 0.5, tumor size less than 5 cm, and tumor number less than 7 as prognostic factors improving survival time in intermediate-stage HCC patients.

Keywords: Hepatocellular carcinoma- intermediate-stage- transarterial chemoembolization- computed tomography

Introduction

Hepatocellular carcinoma (HCC) is a major health problem worldwide, affecting more than 800,000 new patients per year with the highest incidence in Asia and Africa (Akinyemiju et al., 2017; Caines et al., 2020). Well-known risk factors for HCC include hepatitis B and C infection, alcohol intake, and fatty liver disease (Zhang et al., 2021). Since most of the HCC patients are asymptomatic during the early stages, early detection of the tumor by ultrasound is mandatory. However, the ultrasound surveillance for HCC is done by only 20% of patients at risk (Singal and El-Serag, 2015). Therefore, many patients are still diagnosed at intermediate or advanced disease stages (Marin et al., 2015).

Nowadays, multidetector computed tomography (MDCT) is still the most widely used imaging technique to describe the appearance of hepatic tumors treated with locoregional therapies. Moreover, it allows us to accurately assess the response to therapy by providing information on tumor size, number, and invasion. The evaluation of the treatment success is crucial for further treatment decisions and prognosis.

According to the Barcelona Clinic Liver Cancer classification (BCLC), intermediate stage HCC (BCLC-B) is the widest sub-group of patients with diverse liver function, tumor size, and tumor volume (Elshaarawy et al., 2019). Transarterial chemoembolization (TACE) is one of the most common treatment for the intermediate stage HCC (Ayuso et al., 2018; Reig et al., 2021). Contrary to the normal liver, HCC receives blood supply almost entirely from the hepatic artery, thus making TACE effective for HCC treatment. This method consists of transarterial administration of chemotherapy, mostly Doxorubicin, along with iodized oil as a drug carrier, while embolizing particles occlude the tumor-feeding arteries (Ayuso et al.,

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2018; Lucatelli et al., 2021).

Though TACE became a recommended therapy for intermediate-stage HCC in many guidelines (Poon et al., 2015; Omata et al., 2017; 2018), variation in treatment response was shown in prior studies. Only about 16-61% of HCC patients achieved an objective response (Llovet et al., 2002; Forner et al., 2012). This study aimed to determine the overall survival time of intermediate-stage HCC patients who were treated by TACE and prognostic factors improving survival time in these patients.

Materials and Methods

Patient eligibility

Our institutional review board approved this study and waived the requirement for obtaining informed patient consent because of the retrospective nature of the review.

Maharaj Nakorn Chiang Mai medical record database was searched from January 2016 to December 2019 by using an ICD-10 diagnosis search and the following codes: C220 liver cell carcinoma with ICD-9, 5,024 percutaneous ablation of liver lesion or tissue, 8,847 arteriography of other intra-abdominal arteries, 9,925 injection or infusion of cancer chemotherapeutic substance, and 9,929 injection or infusion of other therapeutic or prophylactic substance.

The inclusion criteria were having radiologically confirmed HCC according to the Liver Imaging Reporting and Data system (LI-RADS), being at intermediate stage of HCC according to BCLC, and receiving initial TACE treatment. Patients who underwent other locoregional or systemic therapy were excluded.

TACE procedure

TACE was performed under local anesthesia using the traditional femoral approach and under the guidance of digital subtraction angiography (Infinix, Toshiba, Tokyo, Japan) through the hepatic arteries supplying the tumor. Celiac arteriography was performed using a 5 Fr Yashiro catheter to assess the location, number, size, and blood supply of the target tumor. Superselective TACE was performed, when technically feasible, after identification of hepatic arteries and tumor feeding arteries by using 2.8Fr Renegade HI-FLO catheter (Boston Scientific Corporation, MA, USA) or 2.6Fr Asahi Masters Parkway HF (Asahi INTECC, Pathumthani, Thailand). The embolic emulsion agent, including epirubicin (10–30 mg) and Lipiodol (3-10 mL), was injected into the artery supplying the tumor through a microcatheter. Then, embolization with Gelfoam was done until arterial flow stasis was achieved.

Data collection and image analysis

The patients' demographic (age at the time of diagnosis and sex) and clinical data (survival time, Child PUGH score, underlying viral hepatitis infection, and laboratory data) were extracted from the database.

The aspartate aminotransferase-to-platelet ratio (APRI) was calculated according to the following formula (Wai et al., 2003).

$$APRI = \frac{\frac{AST\ level}{Upper\ level\ of\ normal}}{Platelet\ counts\ (109\ /\ L)}\ x\ 100$$

All pre-TACE CT images were reviewed on a picture archiving and communication system (PACS) using Synapse version 5.0 workstation. One radiologist and one in-training third-year radiology resident evaluated CT findings and made a consensus decision for the characterization of the tumor. Tumor distribution patterns were classified into 3 categories of multiple independent HCC, primary HCC with intrahepatic metastasis representing satellite nodules in the same lobe, and primary HCC with intrahepatic hepatic metastasis in other segments or contralateral lobe (Figure 1). Lobar involvement was classified into unilobar involvement or multilobar involvement. Portal vein thrombosis (PVT) was classified into 3 categories, namely no PVT involvement, PVT within the segmental branch, and PVT within the main branch.

The Up-to-7 criteria (sum of the diameter of the largest tumor (in cm) and the number of tumors) proposed by Mazzaferro et al., was used in this study to determine liver transplantation in HCC (Mazzaferro et al., 2009; Lei et al., 2013).

Statistical analysis

Survival time was calculated from the date of diagnosis to the date of death . Survival curves were created using the Kaplan-Meier method and compared by running log-rank test.

The following prognostic factors were evaluated for estimating patient survival: age, gender, viral hepatitis infection, Child–Pugh class, tumor size, tumor number, Up-to-7 criteria (within and without), tumor distribution pattern (independent HCC, HCC with satellite nodule, HCC with intrahepatic metastasis), tumor involvement extent (unilobar, multilobar) and PVT involvement extent (no involvement, segmental branch involvement, main branch involvement).

All statistical analyses were carried out using SPSS 20.0 (SPSS Inc, Chicago, IL, USA). A P-value of < 0.05 was considered statistically significant.

Results

A total of 675 HCC patients underwent TACE in our hospital over the 8-year period. Out of these patients, 187 ones met our inclusion criteria.

The baseline characteristics of the patients are summarized in Table1. The mean age of patients was 60 years old (ranging from 30-89 years). In terms of gender, the findings revealed that 147 (78.6%) patients were male and 40 (21.4%) patients were female. in terms of underlying viral hepatitis infection, it was found that 81 (43.3%), 52 (27.8%), and 11 (5.9%) patients had hepatitis B (HBV), hepatitis C(HCV), and coinfection of HBV and HCV infection, respectively. The status of HCC patients, based on Child PUGH score, was class A and B in 169 (90.4%) and 18 (9.6%) patients, respectively. There was no patient with class C because in this study.

Table 1. Baseline Characteristic of the Patients with Hepatocellular Carcinoma

Variable		Value (N=187)
Age in years (mean±SD		59.6±0.7
Gender, n (%)	Male	147 (78.6)
	Female	40 (21.4)
Child-Pugh score, n (%)	A	169 (90.4)
	B	18 (9.6)
Viral hepatitis infection, n (%)	HBV	81 (43.3)
	HCV	52 (27.8)
	HBV and HCV	11 (5.9)
AST to platelet ratio (APRI) index	< 0.5	20 (10.8)
	0.5	167 (89.3)
Tumor number	<4	61 (32.6)
	4-7	60 (32.1)
	>7	66 (35.3)
Maximal tumor size (cm)	<3	22 (11.8)
	3-5	59 (31.5)
	>5	106 (56.7)
Up-to-Seven criteria	with	44 (23.5)
	without	143 (76.5)
Lobar involvement	Unilobar	61 (32.6)
	Multilobar	126 (67.4)
Distribution pattern	Multiple independent HCC	96 (51.3)
	Primary HCC with satellite nodules	15 (8.0)
	Primary HCC with intrahepatic metastasis	76 (40.6)
Portal vein thrombosis	Segmental branch	10 (5.3)
	Main branch	8 (4.3)

The CT findings are also summarized in Table 1. The results revealed that 44 (23.5%) patients were within Up-to-7 criteria and 143 (76.5%) patients were without Up-to-7 criteria. The lobar involvement was unilobar and multilobar in 61 (32.6%) and 126 (67.4%), respectively. The distribution pattern of tumor was multiple independent HCC, primary HCC with satellite nodules, and primary HCC with intrahepatic hepatic metastasis in 96 (51.3%), 15 (8.0%), and 76 (40.6%) patients, respectively. PVT was located within the segmental branch and the main branch in 10 (5.3%) and 8 (4.3%) patients, respectively.

It was found that 2 (1.1%) deaths were attributable to a postoperative complication . Kaplan Meier survival analysis indicated that the patients' median survival was 9.9 months (95% confidence interval [CI], 8.3-11.6 months).

The Kaplan-Meier survival curve of patients with APRI is shown in Figure 2. The patients with APRI score less than 0.5 had significantly better overall survival time based on our findings (13.2 months versus 9.9 months, p value = 0.032).

The Kaplan-Meier survival curve and log-rank test showed no significant difference in survival time of patients in terms of lobar involvement (unilobar involvement and multilobar involvement, Figure 3) and tumor distribution patterns (multiple independent HCC, primary HCC with satellite nodules, and primary HCC with intrahepatic hepatic metastasis, Figure 4).

The patients with up-to-7 criteria had better overall outcome than those without the criteria (11.0 months versus 9.3 months, Figure 5). The patients who had more than 7 nodules had significantly poor overall survival time (6.8 months, Figure 6).

The patients who had tumor size larger than 5 cm showed significantly poor overall survival time (9.2 months, Figure 7). The patients' baseline characteristics and pre-TACE CT imaging findings were evaluated using

Table 2. Results of Logistic Regression about Prognostic Factors Associated with HCC

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (in year)	1.195 (0.853-1.675)	0.301		
Sex (male vs female)	0.903 (0.635-1.283)	0.568		
Child-Pugh score (A)[a]	1.122 (0.678-1.856)	0.654		
APRI (<0.5)[b]	0.593 (0.366-0.961)	0.034	0.468 (0.280-0.784)	0.004
Tumor number				
< 4	1			
4-7	1.041 (0.726-1.492)	0.829	1.368 (0.908-2.062)	0.444
> 7	1.980 (1.385-2.831)	0	2.641 (1.678-4.156)	0
The largest tumor size				
< 3 cm	1			
3 – 5 cm	1.030 (0.635-1.671)	0.905	1.673 (0.983-2.849)	0.058
> 5 cm	1.502 (0.950-2.376)	0.082	2.385 (1.318-4.313)	0.004
Up-to-7 criteria (without)[c]	0.677 (0.481-0.952)	0.025	0.817(0.4878-1.371)	0.444
Multilobar involvement	1.066 (0.781-1.457)	0.686		
PVT (Main branch)[e]	1.541 (1.142-2.080)	0.005	1.356(0.86-1.864)	0.061

HBV hepatitis B virus; HCV hepatitis C virus, APRI AST to platelet ratio index; HCC hepatocellular carcinoma, PVT portal vein thrombosis; [a], Child-Pugh A was reference; [b], APRI >0.5 was reference; [c], Within Up-to-7 criteria was reference; [d], Unilobar involvement was reference; [e], No portal vein tumor thrombus was reference

Figure 1. Three Distribution Patterns of Hepatocellular Carcinoma (HCC) on pre-TACE CT Imaging. (a) Axial and (b) coronal arterial CT scan show multiple various size of arterial enhancing lesions in both hepatic lobes, representing multiple independent HCC. Axial (c) and coronal (d) arterial CT scan obtained in a different patient show large solitary enhancing lesion in segment VII (arrow) with surrounding satellite enhancing nodules in right hepatic lobe, representing primary HCC with intrahepatic metastasis in the same lobe. Axial (e) and coronal (f) arterial CT scan obtained in a third patient shows large solitary arterial enhancing lesion (arrow) in right hepatic lobe with multiple enhancing lesions scattering in both hepatic lobes (arrow head), which represent primary HCC with intrahepatic hepatic metastasis in the contralateral lobe.

univariate and multivariate Cox regression analysis to identify the independent prognostic factors for overall survival (Table 2). The result indicated that APRI less than 0.5 could be an independent parameter predicting
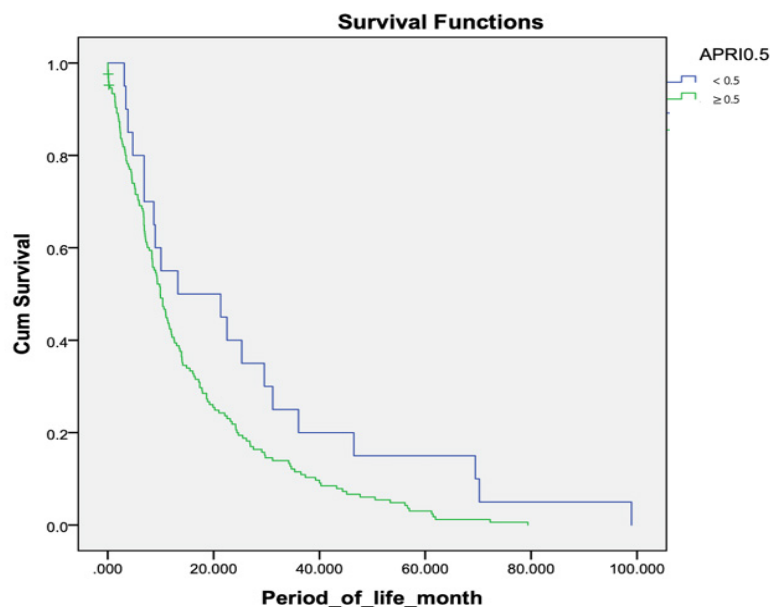

Figure 2. Comparison of Median Survival between Patients with AST to Platelet Ratio Index (APRI) between Less than 0.5 (blue) and beyond 0.5 (green), which showed median survival 13.25 months (95%CI= 0-37.96) and 9.93 months (95%CI= 8.27-11.58), respectively (p = 0.03).
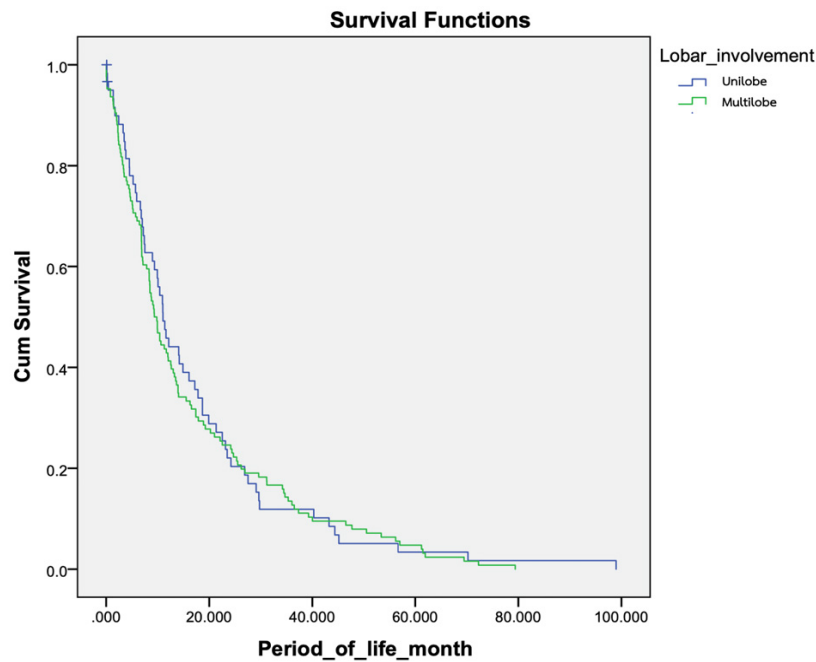
Figure 3. Comparison of Median Survival between Patients with Unilobar Involvement A (blue) and multilobar involvement (green), which showed median survival 11.01 months (95%CI= 8.78-13.23) and 9.33 months (95%CI= 7.74-10.92), respectively (p = 0.68).

overall survival (HR 0.47 95%CI 0.28–0.78 p-value 0.004), while tumor number more than 7 and tumor size larger than 5 cm were found as independent parameters predicting poor overall survival (HR 2.64 95%CI 1.68-4.15 p-value 0.000 and HR 2.38 95%CI 1.32-4.31 p-value 0.004, respectively).

Discussion

Among intermediate-stage HCC patients, survival time after TACE is varied. In our study, the median survival time of patients after TACE was 9.9 months (95% CI: 8.3-11.6). In contrast to our findings, a multicenter study in the United States showed a longer survival time, 17.1 months (White et al., 2017). A systematic review of studies across worldwide showed an average median survival time of 19.4 months (95% CI: 16.2–22.6) (Lencioni et al., 2016). Since there is substantial heterogeneity among patients with intermediate-stage HCC due to notable differences in tumor burden and liver function,
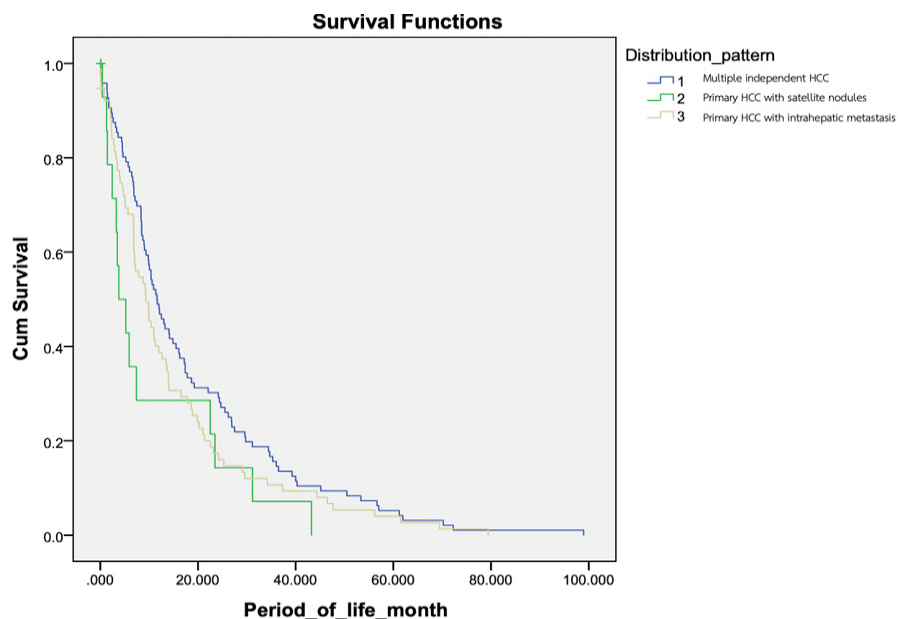

Figure 4. Comparison of Median Survival between Patients in Three Distribution Patterns; multiple independent (blue), primary HCC with satellite nodules (green) and primary HCC with intrahepatic metastasis classification (yellow), which showed median survival 11.6 months (95%CI= 9.0 – 14.1), 3.81months (95%CI= 0.6-7.0) and 9.33 months (95%CI=6.3-12.3), respectively (p = 0.09).
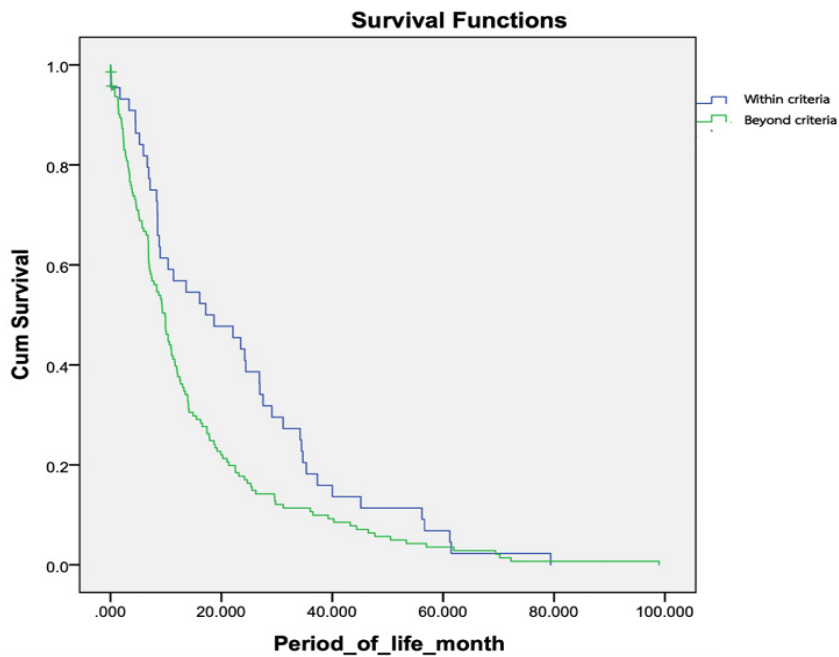
Figure 5. Comparison of Median Survival between Patients within up-to-7 Criteria (blue) and Beyond Criteria (green), which showed median survival 11.01 months (95%CI= 8.78-13.23) and 9.33 months (95%CI= 7.74-10.92), respectively (p = 0.02).

the prognostic parameters (laboratory investigation and CT imaging appearance) were investigated in this study to find out why patients in our studies had lower survival time compared with other studies.

Several laboratory and clinical parameters are applied to estimate the TACE-related risk. The Child-Pugh score is a well-known parameter for evaluating liver function. According to the BCLC/EASL guideline, patients with Child-Pugh score of less than B8 are well suited for

TACE (European Association for the Study of the Liver. Electronic address and European Association for the Study of the, 2018). Accordingly, TACE was performed for patients who had Child-Pugh A or B in this study. No patient with Child-Pugh C was included in our study.

APRI score has been used to evaluate liver fibrosis in hepatitis C patients (Wai et al., 2003). The high value of APRI score correlates with the severity of liver fibrosis. Since liver fibrosis may affect survival time after
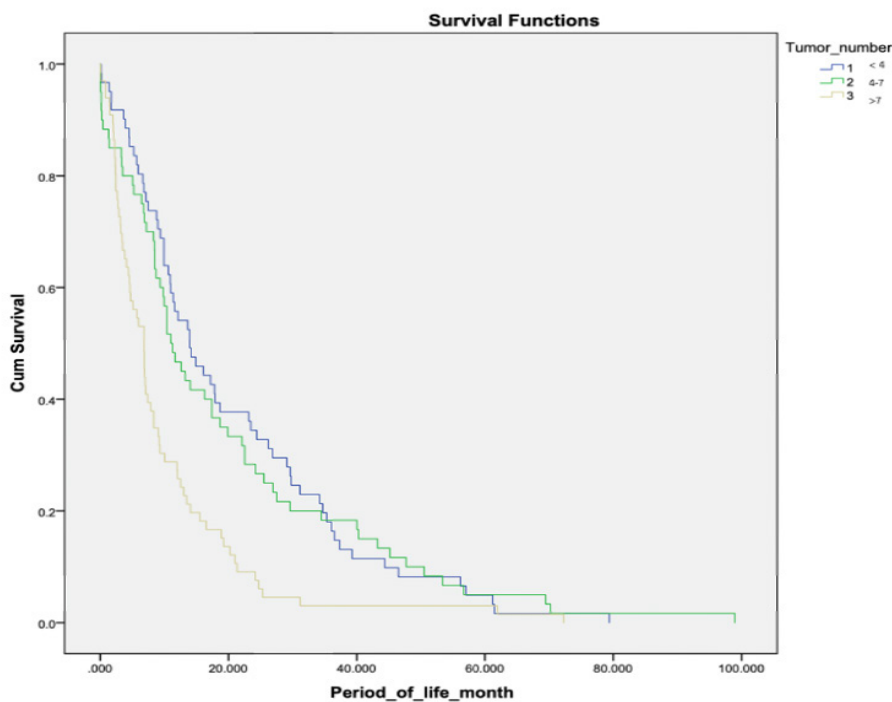

Figure 6. Comparison of Median Survival between Patients with Tumor Number <4 (blue), 4–7 (green) and >7 (yellow) lesions, which showed median survival 13.93 months (95%CI= 9.05 – 18.82), 11.01months (95%CI= 8.12-13.90) and 6.83 months (95%CI=5.07-8.60), respectively (p < 0.001).
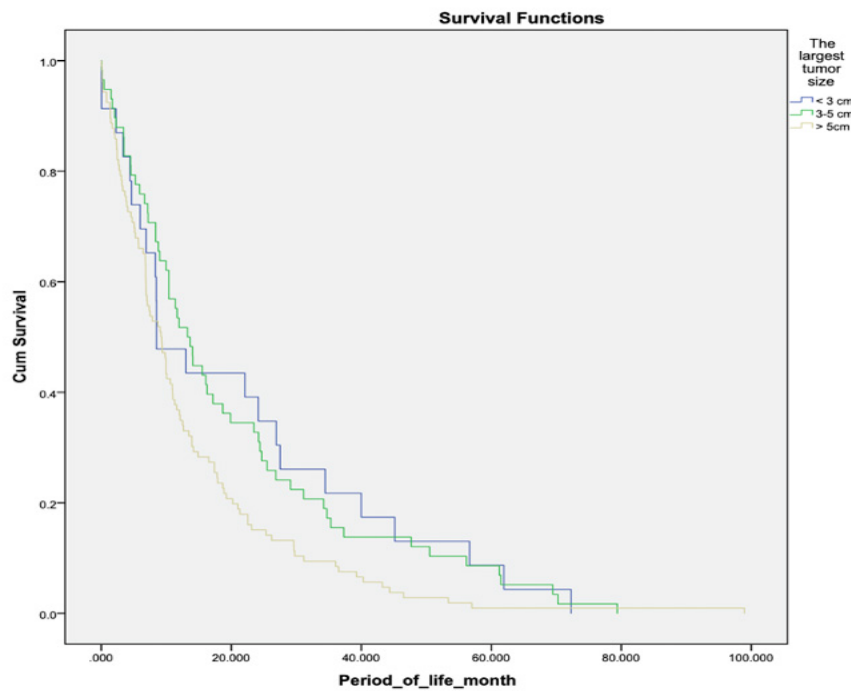
Figure 7. Comparison of Median Survival between Patients with Largest Tumor Size between <3 (blue), 3-5 (green) and >5 (yellow) cm, which showed median survival 8.48 months (95%CI= 1.32-15.63), 13.24 months (95%CI= 9.89-16.6) and 9.2 months (95%CI=6.98-11.42), respectively (p = 0.02).

interventional procedures, APRI should be regarded as a potential prognostic indicator for intermediate-stage HCC patients who received TACE. In our study, the APRI score was found as a significant prognostic factor. The patients with APRI < 0.5 had longer survival time compared with those with APRI > 0.5. Prior studies also showed the prognostic value of APRI. Kao (2011) used APRI as a prognostic factor in patients with small HCC who received radiofrequency ablation (Kao et al., 2011). Gui-Qi (2019) used the cutoff value of 0.50 for APRI to predict the prognosis of HCC after postoperative adjuvant TACE and found that patients with high APRI had poorer survival rate than those with low APRI (Zhu et al., 2019).

According to BCLC, intermediate-stage HCC patients had the following characteristics: Child-Pugh A-B, performance status 0, tumor size larger than 3 cm or multifocal HCC, no vascular invasion, no nodal disease, and no distant metastatic disease. Heterogeneity of tumor burden and liver function in this stage causes a wide range of survival outcome in the sufferers. We found that patients with tumor size larger than 5 cm or tumor number more than 7 had poorer survival outcome.

Mazzaferro et al., (2009) proposed Up-to-Seven criteria for liver transplantation, with the cut-off value of seven being the sum of the size of the largest tumor diameter and the number of tumor nodules. Kimura et al., (2017) sub-classified intermediate-stage HCC by using Up-to-Seven criteria and serum tumor marker. He found that patients without Up-to-Seven criteria with AFP more than 100 ng/ml had poor overall survival rate. Although Up-to-Seven criteria have been analyzed all over the world, they have not been as widely accepted to use as survival predictor score yet (Mazzaferro et al., 2009; Lei et al., 2013; Kimura et al., 2017). Based on this score,

our patients with Up-to-Seven criteria had better median survival time than patients without Up-to-Seven criteria (11.0 months versus 9.3 months). However, the median survival of patients with Up-to-Seven criteria was less than that reported in previous studies (11.0 months versus 3.5 years) (Kimura et al., 2017).

There were a few limitations in this study. First, it was a retrospectively study. Second, the detail of TACE technique and sequencing were not explored, which could be another factor affecting lower survival outcome (Miyayama et al., 2021). Third, our study was done in one healthcare center. A multicenter study with a larger number of patients is recommended for future analyses

In conclusion, our patients with intermediate-stage HCC who underwent TACE had a lower median survival time compared to previous studies. However, we identified APRI less than 0.5, tumor size less than 5 cm, and tumor number less than 7 as prognostic factors improving survival outcome in HCC patients.

Author Contribution Statement

This study was designed by Nakarin Inmutto and Natthaphong Nimitrungtawee. The data were collected and analyzed by Oranit Puttisri. The manuscript was written by Nakarin Inmutto and Natthaphong Nimitrungtawee.

funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors do not have any conflicts of interest.

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