ORIGINAL ARTICLE

Efficacy of First-line Systemic Treatment in Unresectable or Advanced Hepatocellular Carcinoma in Thailand: A Retrospective Study

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Background: First-line systemic treatments for unresectable or advanced hepatocellular carcinoma (HCC) are gradually increasing. In developing countries, including Thailand, there are limitations to access some effective treatments. We aim to explore the real-world efficacy of first-line systemic therapy in patients with unresectable or advanced hepatocellular carcinoma.

Objective: The primary objective was the progression-free survival (PFS) of the tyrosine-kinase inhibitors (TKIs) group compared with the FOLFOX group. Secondary objectives included PFS, overall survival (OS), response rate by treatment types, and the identification of prognostic factors associated with PFS and OS.

Materials and Methods: A single-center, retrospective study was conducted on patients diagnosed with unresectable or advanced hepatocellular carcinoma who received first-line systemic therapy between January 2017 and December 2022.

Results: In the overall population (n=215), most patients were male, had ECOG performance status 0-1, Child-Pugh score A, viral-hepatitis-associated disease, and Barcelona Center of Liver Cancer (BCLC) stage C. In the TKIs group (n=134), the median PFS was 3.4 months, compared with 2.9 months in the FOLFOX group (n=68) (HR=0.73, 95% CI 0.54 to 0.99, p=0.044). The median PFS was 3.0 months, 4.8 months, and 11.7 months in the sorafenib (n=108), lenvatinib (n=26), and atezolizumab plus bevacizumab groups (n=13), respectively. The median OS was 8.1, 9.2, 11.0, and 19.4 months in the FOLFOX, sorafenib, lenvatinib, and atezolizumab plus bevacizumab groups, respectively. The objective response rates were 5.8%, 1.9%, 15.4%, and 30.8% in the FOLFOX, sorafenib, lenvatinib, and atezolizumab plus bevacizumab groups, respectively. The factor associated with PFS was viral hepatitis-associated disease, while the factors associated with OS were Child-Pugh score, ALBI score, and macrovascular invasion status.

Conclusion: TKIs provide longer PFS. FOLFOX demonstrates similar PFS but higher response rates and disease control compared to sorafenib. The viral-related disease was associated with PFS, while child-Pugh score, ALBI score, and vascular invasion were the factors associated with OS.

Keywords: Hepatocellular carcinoma; HCC; FOLFOX; Sorafenib; Lenvatinib; First-line

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Primary liver cancer is the sixth most common cancer and the third-largest contributor to cancer-related mortality worldwide[(1)]. The most common histology (approximately 80%) is hepatocellular carcinoma (HCC)[(2)]. In Thailand, HCC is the most frequently diagnosed among all cancers and the leading cause of death in men[(1)]. Hepatitis B (HBV) infection, chronic hepatitis C (HCV) infection, excessive alcohol consumption, and metabolic syndrome are the major

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risk factors for HCC[2].

The treatment of HCC depends on the stage of the disease. There are many classifications of staging in HCC; however, Barcelona-Clinic Liver Cancer (BCLC) staging is the most commonly used globally. The BCLC staging uses the performance status of the patients, hepatic function, and disease extension for stratified HCC patients. Tumor resection, liver transplantation, local radio-ablation, and transarterial chemoembolization (TACE) are recommended treatments for early-stage HCC (BCLC A and B). In patients with a good performance status and good hepatic function but the disease invasion to the portal vein or extra-hepatic disease spreading (BCLC-C), systemic treatments play a role in this stage[3].

HCC was considered resistant to anticancer chemotherapy, FOLFOX4 did not provide superior overall survival (OS) to single-agent doxorubicin, even increase in progression-free survival (PFS) and objective response rate (ORR)[4]. After that, targeted drugs (multi-kinase inhibitors) were developed to treat unresectable and advanced HCC, such as sorafenib and lenvatinib. Sorafenib demonstrated PFS and OS superior to placebo[5], while lenvatinib showed non-inferior OS to sorafenib[6].

To date, atezolizumab plus bevacizumab was demonstrated to be the most effective first-line treatment, according to an IMbrave150 study. It provided a median OS of 19.2 months and a median PFS of 6.0 months compared to sorafenib[7]. The other preferred immunotherapy regimens are durvalumab plus tremelimumab, or single-agent durvalumab, providing OS benefits compared to sorafenib[8].

Despite ongoing development of standard frontline therapy for HCC to increase the survival of patients, the accessibility to treatments is still limited, especially in developing countries. Thus, our study aims to demonstrate the real-world efficacy of first-line systemic therapy, including chemotherapy (FOLFOX).

Materials and Methods

Study design and patients eligibility

The present study was a single-center retrospective, including patients diagnosed with unresectable or advanced hepatocellular carcinoma confirmed by histology or clinical features based on the American Association for the Study of Liver Disease criteria (AASLD) for patients with cirrhosis (typical imaging plus AFP) at Srinagarind Hospital between January 2017 and December 2022. The inclusion criteria were age ≥18, receiving first-line systemic treatment for unresectable or advanced hepatocellular carcinoma, and allowance for previous local therapies. Exclusion criteria included active second-primary cancer within the past 5 years, mixed HCC and cholangiocarcinoma (CCA), as well as incomplete clinical or follow-up data for patients.

Baseline characteristics, types of therapies, and treatment outcomes were collected from electronic medical records (EMR) and outpatient department (OPD) cards. Progression-free survival (PFS) was calculated from initiating first-line systemic treatment until disease progression or death. Overall survival is defined from the start of systemic therapies until death from any cause. Investigators evaluated tumor response by CT or MRI at intervals according to local practice, using RECIST 1.1 criteria.

This study was approved by the Human Research Ethics Committee of Khon Kaen University, Khon Kaen, Thailand (HE661006).

Objectives

The primary objective:

PFS of TKIs (sorafenib and lenvatinib) group compared with FOLFOX group.

The secondary objectives:

PFS by types of treatments compared with FOLFOX.

OS by types of treatment compared with FOLFOX.

Response rate.

Prognosis or predictive factors associated with PFS and OS in unresectable or advanced HCC.

Sample size

The sample size was 134 patients (67 in the TKIs group and 67 in the FOLFOX group), calculated based on the assumption of a hazard ratio (HR) of 0.58 for PFS in the TKIs group and 0.8 in the FOLFOX group, with a statistical power of 80% and an alpha value of 0.05.

Statistical analysis

The patients' baseline characteristics were reported using descriptive statistics. Pearson’s Chi-squared, Fisher's exact tests, oneway-ANOVA, and Kruskal Wallis test were employed to assess the differences in patient baseline characteristics. The Kaplan-Meier method was utilized to estimate Progression-Free Survival (PFS) and Overall Survival (OS). Hazard ratios and 95% confidence intervals (95% CI) were determined using a Cox proportional-hazards model. Patients who were alive at the last follow-up were censored for OS analysis.

Regarding factors associated with PFS and OS, a flexible parametric regression model was employed, which included both univariate and multivariate testing. An alpha <0.05 was considered statistically significant. All statistical analyses were performed using Stata software version 16.1

Results

From January 2017 to December 2022, 313 patients diagnosed with HCC and receiving first-line systemic

therapy were included. Ninety-eight patients were excluded from the study, as shown in Figure 1. Finally, 215 patients were included, with 108 patients receiving sorafenib as first-line systemic therapy. Additionally, 26, 13, and 68 patients were treated with lenvatinib, atezolizumab plus bevacizumab, and FOLFOX, respectively. The sorafenib group combined with the lenvatinib group is referred to as the TKIs group (n=134). The overall baseline characteristics of the patients are presented in Table 1. The median age at the time of disease onset was 62.5, 62, 57, and 58 in the sorafenib, lenvatinib, atezolizumab plus bevacizumab, and FOLFOX groups. Most cases were male with an ECOG performance status of 0-1, except the lenvatinib group, which had patients with ECOG 2, up to 19.2%. The primary etiology of HCC in the study was viral-associated HCC, more than non-viral disease. BCLC score of C, Child-Pugh score of A, and ALBI score of 1 or 2 were mainly included in the present study. Around half of the patients had AFP ≥400, major vascular invasion, and extrahepatic disease extension. The lung, liver, and bone were the most common sites of metastatic disease. Thirty-five to fifty percent of patients had received prior local treatment, mostly TACE. The median dose of sorafenib was 400 mg/day and lenvatinib was 10 mg/day, with full doses of atezolizumab and bevacizumab. All patients in the FOLFOX group received FOLFOX4.

Primary objective: PFS of TKIs compared with FOLFOX

As of the date of the data cutoff (March 31, 2023), the median duration of follow-up was 28.3 months. In the overall population (n=215), the median PFS and OS were 3.3 months (95% CI 2.9 to 3.8) and 9.5 months (95% CI 8.5 to 11.8), respectively (Supplement Figure 1). In the TKIs group, the median PFS was 3.4 months compared to 2.9 months in the FOLFOX group (Hazard ratio (HR) for PFS was 0.73; 95% confidence interval [CI], 0.54 to 0.99; p=0.044) (Figure 2).

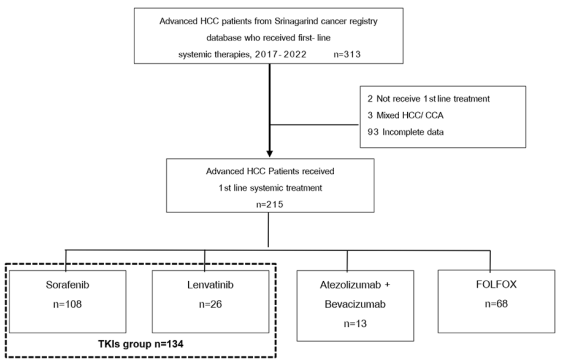


Figure 1. Consort diagram.

Secondary objectives

PFS by types of treatments compared with FOLFOX.

The median PFS was 3.0 months in the sorafenib group and 2.9 months in the FOLFOX group (HR, 0.79; 95% CI, 0.58 to 1.09, p=0.16). In the Lenvatinib group, the median PFS was 4.8 months (HR, 0.48; 95% CI, 0.29 to 0.89, p=0.005). The median PFS in the atezolizumab plus bevacizumab group was 11.7 months (HR, 0.27; 95% CI, 0.13 to 0.57, p=0.001), as shown in Figure 3.

OS by types of treatments compared with FOLFOX.

At the cutoff date, 7 patients in the atezolizumab plus bevacizumab group, 11 patients in the lenvatinib group, and 90 patients in the sorafenib group had died, compared to 57 patients in the FOLFOX group. The median overall survival was 9.2 months (HR, 0.93; 95% CI, 0.67 to 1.30, p=0.68), 11 months (HR, 0.58; 95% CI, 0.31 to 1.12, p=0.11), and 19.4 months (HR, 0.47; 95% CI, 0.22 to 1.04, p=0.06) in the sorafenib, lenvatinib, and atezolizumab plus bevacizumab groups, respectively, compared to the FOLFOX group (Figure 4).

Response rate

The objective response rates were 30.8% with atezolizumab plus bevacizumab, 15.4% with lenvatinib, 5.8% with FOLFOX, and 1.9% with sorafenib. The patients exhibited a complete response of 23.1%, 3.9%, 2.9%, and 0% in the atezolizumab plus bevacizumab, lenvatinib, FOLFOX, and sorafenib groups, respectively. The disease control rates were 69.3%, 73.1%, 44%, and 34.6% in the atezolizumab plus bevacizumab, lenvatinib, sorafenib, and FOLFOX groups, respectively (Table 2).

Prognosis or predictive factors associated with PFS and OS in unresectable or advanced HCC

The factors significantly associated with PFS in unresectable or advanced HCC was viral-related disease. The median PFS was 2.6 months in non-viral related disease and 3.7 months in viral related disease (HR=0.62, 95% CI 0.44 to 0.88, p=0.01) (Table 3 and Supplement Figure 2), a finding that persisted as significant in multivariate analysis after adjusting for sex, Child-Pugh score, ALBI score, and macrovascular invasion status.

The factors associated with OS included Child-Pugh score B compared with A (HR=1.83, 95% CI 1.14 to 2.94, p=0.011), ALBI score 2 compared with 1 (HR=1.61, 95% CI 1.17 to 2.21, p=0.004), and vascular invasion compared with no vascular invasion (HR 1.42, 95% CI 1.04 to 1.93, p=0.026) (Table 3 and Supplement Figure 3).

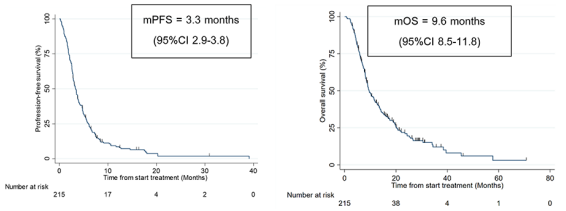
Discussion

The options for first-line systemic therapy for unresectable or advanced HCC are gradually increasing.

Table 1. Baseline characteristics

	Sorafenib, n=108 (%)	Lenvatinib, n=26 (%)	TKIs, n=134 (%)	Atezolizumab+Bev n=13 (%)	FOLFOX, n=68 (%)	p-value
Median age (yr, IQR)	62.5 (58 to 66)	62 (53 to 68)	62 (58 to 66)	57 (56 to 66)	58 (52 to 62)	0.61
Gender						
Male	89 (82.4)	22 (84.6)	111 (82.8)	10 (76.9)	60 (88.2)	0.46
Female	19 (17.6)	4 (15.4)	23 (17.2)	3 (23.1)	8 (11.8)	
ECOG						
0	8 (7.4)	1 (3.9)	9 (6.7)	0	3 (4.4)	0.92
1	98 (90.7)	20 (76.9)	118 (88.0)	13 (100)	64 (94.1)	
2	2 (1.9)	5 (19.2)	7 (5.3)	0	1 (1.5)	
Comorbid						
DM	23 (21.3)	5 (19.2)	28 (20.8)	1 (7.7)	2 (2.94)	0.16
HT	14 (13.0)	3 (11.5)	17 (12.7)	1 (7.7)	2 (2.94)	
DLP	5 (4.6)	0	5 (3.7)	0	0	
Etiology						
HBV	35 (32.4)	12 (46.2)	47 (35.1)	7 (53.9)	25 (36.8)	0.23
HCV	45 (41.7)	6 (23.1)	51 (38.1)	4 (30.8)	27 (39.7)	
Both HBV and HCV	4 (3.7)	1 (3.9)	5 (3.7)	0	4 (5.9)	
Non-viral	24 (22.2)	7 (26.8)	31 (23.1)	2 (15.3)	12 (16.6)	
Diagnosis						
Imaging+AFP	62 (55.8)	22 (84.6)	84 (62.7)	12 (92.3)	58 (85.3)	0.007
Tissue	46 (44.2)	4 (15.4)	50 (37.3)	1 (7.7)	10 (14.7)	
Child-Pugh score						
A	97 (89.8)	22 (84.6)	119 (88.8)	13 (100)	60 (88.2)	0.44
B	11 (10.2)	4 (15.4)	15 (11.2)	0	8 (11.8)	
ALBI score						
1	46 (42.6)	5 (19.2)	51 (38.0)	11 (84.6)	27 (39.7)	0.005
2	60 (55.6)	20 (76.9)	80 (59.7)	2 (15.4)	41 (60.3)	
3	2 (1.8)	1 (3.9)	3 (22.3)	0	0	
BCLC						
B	2 (1.9)	1 (3.8)	3 (2.2)	1 (7.3)	3 (4.4)	0.005
C	104 (96.2)	25 (96.2)	129 (96.3)	12 (92.7)	63 (92.6)	
D	2 (1.9)	0	2 (14.9)	0	0	
AFP						
<400	59 (54.6)	12 (46.2)	71 (53.0)	7 (53.8)	27 (39.7)	0.19
≥400	49 (45.4)	14 (53.8)	63 (47.0)	6 (46.2)	41 (60.3)	
Macrovascular invasion	60 (55.6)	14 (53.8)	74 (55.2)	6 (46.2)	32 (47.0)	0.49
Tumor diameter (median, IQR)	6.75 (3.9 to 10.2)	6.35 (3.0 to 10.9)	6.45 (3.7 to 10.3)	6.65 (3.6 to 13.0)	7.5 (3.9 to 12.0)	0.53
Extra-hepatic extension	46 (42.6)	11 (42.3)	57 (42.5)	8 (61.5)	34 (50.0)	0.31
Metastasis organ						
Liver	4 (3.7)	3 (11.5)	7 (5.2)	0	0	0.57
Lung	25 (23.1)	8 (30.7)	33 (24.6)	5 (38.5)	16 (23.5)	
Bone	6 (5.6)	2 (7.6)	8 (6.0)	1 (7.7)	2 (2.9)	
Peritoneal	6 (5.6)	0	6 (4.4)	1 (7.7)	10 (14.7)	
Prior treatment						
Surgery	19 (17.6)	1 (3.8)	20 (14.9)	0	11 (16.1)	0.28
TACE	48 (44.4)	9 (34.6)	57 (42.5)	7 (53.9)	21 (30.9)	0.16

Currently, several drugs, such as sorafenib, lenvatinib, and atezolizumab plus bevacizumab, as well as durvalumab with or without tremilimumab, along with systemic chemotherapy, are recommended for selected patients[4-8]. This study is a retrospective analysis reporting real-world data on the first-line systemic treatment of HCC, including



Supplementary Figure 1. The median PFS and OS in all popoulation (n=215).

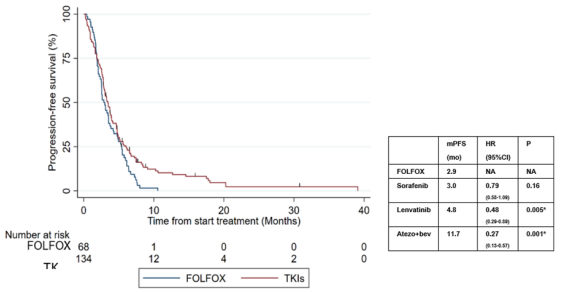


Figure 2. Progression-free survival of TKIs group compare with FOLFOX group.

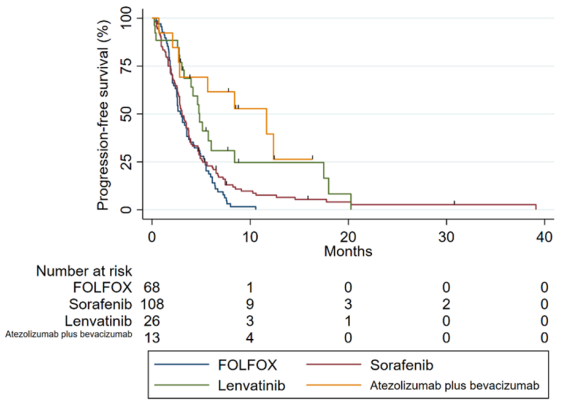


Figure 3. Progression-free survival by types of treatments compared with FOLFOX.

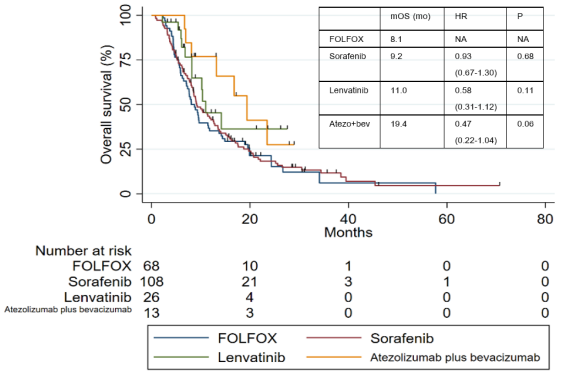


Figure 4. OS by types of treatments compared with FOLFOX.

Table 2. Response rate by type of treatment

Type of treatment	Response (%)	ORR (%)	DCR (%)
Atezolizumab plus bevacizumab	CR 23.1	30.8	69.3
	PR 7.7		
	SD 38.5		
Lenvatinib	CR 3.9	15.4	73.1
	PR 11.5		
	SD 57.7		
FOLFOX	CR 2.9	5.8	44.0
	PR 2.9		
	SD 38.2		
Sorafinib	CR 0	1.9	34.6
	PR 1.9		
	SD 32.7		

chemotherapy (FOLFOX).

In the present study, the median PFS of TKIs was longer than that of FOLFOX (3.4 vs. 2.9 months) with an HR of 0.73, and a statistically significant p=0.044. This PFS is consistent with a previous study in Thailand, which reported a PFS of 5.46 months for the sorafenib group compared to 3.33 months for the FOLFOX group[9]. Additionally, a retrospective study in northeastern Thailand by Chayangsu C., et al., reported a PFS for the FOLFOX group that is similar to our findings (2.9 months)[10]. These consistent data indicate the benefits of sorafenib and FOLFOX in the Asian population, which may be attributed to similar geographic and etiological factors of HCC in this region.

In the present study, the Atezolizumab plus Bevacizumab and Lenvatinib group demonstrated a significantly improved PFS compared to FOLFOX, consistent with previous data[6,7]. The median PFS for Atezolizumab plus Bevacizumab in our study was 11.7 months, significantly higher than the 6.8 months reported in the IMbrave150 study. This discrepancy may be attributed to selection bias, a small sample size, and the high prevalence of viral-related etiology of HCC in our cohort (94.7%). In contrast, OS and ORR were similar to those reported in historical trials, indicating consistent efficacy across different studies.

Lenvatinib has demonstrated lower PFS, OS, and ORR than the Reflect study[6,11].

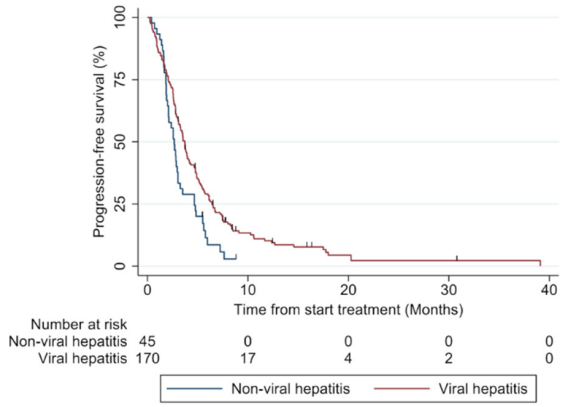
This discrepancy may be attributed to the characteristics of the patient in our study, which included approximately 20% of patients with an ECOG performance status of 2 and 76.9% of patients with an ALBI score of 2. Additionally, the smaller sample size of our study likely contributed to these differences. Furthermore, the dosage of lenvatinib administered may also have impacted these results.

Sorafenib demonstrated outcomes closely aligning with those observed in the Asia-Pacific Sharp study[12]. The TTP, and OS were 2.8 and 6.5 months compared to 3.0 and 9.2

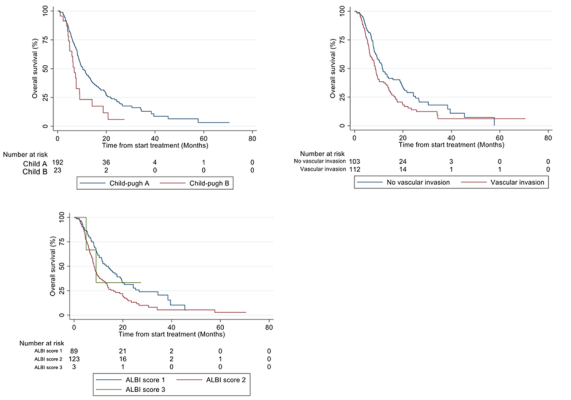
Table 3. Prognosis or predictive factors associated with PFS and OS in unresectable or advanced HCC

	Univariate PFS			Multivariate PFS	Univariate OS			Multivariate OS
	HR	95% CI	p-value	HR; p-value	HR	95% CI	p-value	HR; p-value
Female	0.95	0.64 to 1.40	0.82		0.72	0.47 to 1.09	0.11	
Child B	1.23	0.80 to 1.91	0.36		1.83	1.14 to 2.94	0.01*	1.53; 0.10
ALBI=2	1.17	1.87 to 1.55	0.30		1.63	1.19 to 2.25	0.003*	1.27; 0.12
Viral hepatitis	0.62	0.44 to 0.88	0.01*	0.62; 0.007*	0.89	0.61 to 1.32	0.54	
AFP>400	0.94	0.71 to 1.24	0.66		1.09	0.81 to 1.50	0.55	
Extrahepatic extension	0.98	0.74 to 1.30	0.91		0.88	0.65 to 1.20	0.44	
Vascular invasion	1.18	0.89 to 1.56	0.24		1.45	1.06 to 1.97	0.019*	1.34; 0.07
Previous TACE	0.99	0.75 to 1.32	0.99		0.87	0.61 to 1.13	0.23	

* Statistical significant



Supplementary Figure 2. Prognostic factor associated with PFS.



Supplementary Figure 3. Prognostic factors asscociated with OS.

months of PFS and OS in our study. Notably, OS showed a slight increase in our investigation, potentially attributable to advancements in cirrhosis management and increased utilization of subsequent therapies for advanced HCC.

In our study, FOLFOX did not show a significant difference in PFS compared to the EACH study, with both studies reporting a PFS of 2.9 months. However, the overall survival (OS) was slightly higher in our study, at 8.1 months compared to 6.8 months in the EACH study[4,13]. This improvement may be attributed to enhanced supportive care for cirrhosis patients and subsequent treatments for advanced HCC. When comparing our results to Asia-Pacific SHARP study, FOLFOX demonstrated an improvement in overall survival, with 8.1 months in the FOLFOX group versus 6.5 months in the placebo arm of the Asia-Pacific SHARP study. Despite this, the overall survival of untreated HCC BCLC-C patients in Italy was reported to be 7 months[14]. These differences highlight the potential impact of regional variations in supportive care and treatment practices on patient outcomes. Additionally, the health coverage scheme may influence OS outcomes in each group by affecting access to subsequent treatments (Supplement Table 1).

Supplementary Table 1. Subsequent treatments

	FOLFOX (n=68)	Sorafenib (n=108)	Lenvatinib (n=26)	Atezo+Bev (n=13)
Second-line				
TACE	0	1	2	0
Sorafenib	3	0	0	0
Lenvatinib	0	0	0	3
Regorafenib	0	14	0	0
Cabozantinib	0	0	1	1
Immunotherapy	0	7	7	0
FOLFOX	0	14	0	1
Third-line				
Regorafenib	0	5	3	0
Cabozantinib	0	1	1	0
Immunotherapy	0	3	2	0
FOLFOX	0	3	2	0

Differences in health coverage can lead to variations in the availability and affordability.

The prognostic factor associated with PFS in unresectable or advanced hepatocellular carcinoma was

viral-related disease. In addition, the prognostic factors associated with OS were Child-Pugh score, ALBI score, and macro-vascular invasion. These results are likely the study of Tandon et al. that reported portal vein thrombosis, tumor size, a-fetoprotein and Child–Pugh class are the prognostic factor for OS[15]. However, our study cannot show the association between increased baseline AFP over 400 ng/mL, BCLC staging, extra-hepatic disease and mortality, inconsistent with a previous study[10,16,17]. These factors did not show statistically significant in the multivariate analysis due to limited sample size.

The present study has strength because it is a large dataset of real-world data on systemic treatment for unresectable or advanced Hepatocellular Carcinoma, including chemotherapy (FOLFOX), and patients who underwent previous local therapies. However, there were many limitations. Followings retrospectively collected data from a single center, with no restrictions scheduled in clinical and imaging follow-up, the uncontrollable bias of the baseline population that affected the results, and few patients to estimate a significant difference in some results that might affect the efficacy outcomes.

We suggest that further study should be multi-center, prospective, and more sample size that might be shown the accurate efficacy and significant factors associated with the survival of patients.

Conclusion

TKIs provide a minimal but significantly longer PFS than FOLFOX. The viral-related disease was associated with PFS, while child-Pugh score, ALBI score, and vascular invasion were the factors associated with OS.

What is already known on this topic?

The PFS and OS in the patient with unresectable or advanced HCC depend on first-line systemic treatment. In Asia had poorer outcome than the rest of the world.

What this study adds?

This is the largest study focused on HCC patients. We report the real-world efficacy of first-line systemic treatment included chemotherapy (FOLFOX). This might be the largest real-world evidence of chemotherapy in Asian population.

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Potential conflicts of interest

The authors declare no conflict of interest.

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