

Systemic Treatment of Hepatocellular Carcinoma: A Retrospective Analysis of Single-Center Experience

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Received: 10 Sep 2026

Accepted: 07 Oct 2026

Published: 17 Oct 2026

J Short Name: JJGH

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Keywords:

Hepatocellular Carcinoma (HCC); Advanced Stage; Systemic Treatment

Citation:

Ahmad Mahrous Dewidar Eissa, Systemic Treatment of Hepatocellular Carcinoma: A Retrospective Analysis of Single-Center Experience. Japanese Jour of Gastro and Hepatology® 2026; V11(1): 1-12

1. Abstract

1.1. Background

With the emergence of new systemic therapies there has been a substantial change in treatment options for hepatocellular carcinoma (HCC). The aim of this study was to assess treatment patterns and outcomes in HCC patients with intermediate and advanced stage disease who have received systemic treatments

1.2. Methods

HCC patients with intermediate or advanced disease who received at least one dose of systemic therapy between January 1, 2022, to May 31, 2026 in our centre were included. Patient characteristics, treatment patterns, overall survival (OS), progression-free survival, and reasons for treatment discontinuation were retrospectively analysed in all patients.

1.3. Results

Of the 35 total patients included, 62.9% of cases had stage III, and 28.6% had stage IV. 25.7% had a positive history of HBV, versus 17.1% for positive HCV. The 1st line treatment implemented to 88.6% of cases 42.9% of them received (Atezolizumab & bevacizumab) treatment, and same for (Lenvatinib) treatment. After treatment the median PFS was 5 months. The median overall survival duration was (10) months.

1.4. Conclusions

The findings demonstrate that outcomes of systemic treatment in advanced HCC in real-world practice may differ from those observed in randomized clinical trials because of differences in tumour stage, portal vein invasion, AFP, liver function, viral aetiology, and access to subsequent therapy.

2. Introduction

Hepatocellular carcinoma (HCC) represents a major global health

burden and remains one of the leading causes of cancer-related mortality worldwide, ranking third among causes of cancer death according to the World Health Organization (WHO) [1,2]. Curative approaches, including surgical resection and liver transplantation, can provide favourable outcomes in appropriately selected patients. However, only a minority of individuals are candidates for these interventions because HCC is frequently diagnosed at an advanced stage, when the likelihood of long-term survival is substantially reduced [3-5].

The therapeutic landscape for advanced HCC has changed considerably with the development of systemic therapies, particularly immune-based treatment strategies [6-10]. In the IMbrave150 trial, the combination of atezolizumab and bevacizumab demonstrated a significant overall survival (OS) advantage over sorafenib in patients with advanced HCC. At a median follow-up of 17.6 months, the median OS with atezolizumab plus bevacizumab reached 19.2 months [9]. Similarly, the HIMALAYA trial evaluated the combination of durvalumab and tremelimumab and reported improved OS compared with sorafenib. Median OS was 16.4 months after a median follow-up of 49.12 months, with 25.2% of patients remaining alive at four years [10]. These findings have established both immunotherapy-based combinations as important first-line treatment options for patients with advanced HCC.

The Barcelona Clinic Liver Cancer (BCLC) classification is widely applied in clinical practice to categorize disease stage, estimate prognosis, and guide treatment selection in patients with HCC. Within this framework, patients with intermediate-stage disease are categorized as BCLC stage B, whereas those with advanced disease are classified as BCLC stage C. Although the BCLC system has undergone validation and has demonstrated utility in prognostic assessment, its ability to accurately discriminate outcomes among

patients with intermediate- and advanced-stage HCC in the contemporary era of widespread systemic therapy has not been adequately investigated [11-14].

3. Method

This is a single center retrospective observational study to evaluate patient characteristic, treatment trends, and clinical outcome for HCC patients with intermediate or advanced disease who received at least one dose of systemic therapy between January 1, 2022 to May 31, 2026 in our center were included.

4. Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA). The study variables were summarized using appropriate descriptive statistical methods. Categorical variables were expressed as frequencies and corresponding percentages. For continuous variables, data following a parametric distribution were summarized using the mean and standard deviation (SD), while variables with a non-parametric distribution were described using the median and range.

Quantitative data included in the study first tested for normality by One-Sample Kolmogorov-Smirnov test in each study group then inferential statistic tests selected.

The Kruskal Wallis test used to compare non parametric quantitative data between more than two independent groups.

The Mann-Whitney test used to compare non parametric quantitative data between two independent groups.

Wilcoxon tests used in comparing non parametric quantitative data between two groups of dependent data

Chi square test used to compare between two of more than two qualitative groups.

Bivariate Spearman's correlation test to test the association between quantitative non parametric variables

Kaplan -Meier test for survival analysis.

The P-value < 0.05 was considered as statistically significant

5. Results

Among study group the mean age was (69.5±8.5) years 88.6% of them were males versus 11.4% of them were females. As regards stage of tumour 62.9% of cases had stage III, and 28.6% had stage IV. 40% of cases showed portal vein thrombosis, with 25.7% had a positive history of HBV, versus 17.1% for positive HCV. Majority of cases 80% were diagnosed by radiological methods. 88.6% of cases received 1st line of treatment, 25.7% of them go to 2nd line of treatment, 8.6% of cases go through 3rd line of treatment, 5.7% of cases needed to 4th line but 2.6% needed 5th line of treatment. as regards laboratory investigation the median AFP level at diagnosis time it was (173), the median albumin level was (33.3), median INR was (1.2), total bilirubin was (14.7) the median child score was 6. See Table 1.

The 1st line treatment implemented to 88.6% of cases 42.9% of them received (Atezozolimab & bevacizumab) treatment, and

same for (Lenvatinib) treatment. After treatment the median PFS was 5 months ranged between (1-48) and median AFP of (15.5) ranged between (0 and 17000). 33.4% had side effects 25.7% had fatigue, 2.9% for each vomiting, and skin rash. See Table 2. One fourth of cases needed for the 2nd line treatment (25.7%), 44.4% of them received (Caboazanatinib), and 33.3% for (Lenvatinib). After treatment the median PFS was 3.5 months ranged between (1-9) and median AFP of (22) ranged between (2 and 59412). 44.4% had side effects 33.3% had skin rash, 11.1% had diarrhea. see Table 3. Few cases needed for the 3rd, 4th, and 5th lines of treatment (8.6%, 5.6%, and 2.6%), After treatment the median PFS was (3, 2, and 8) for each line respectively. See Table 4. As regards tumour management way, 8.6% of cases implement RFA, and same did TARE. 2.9% of cases implemented TACE. Table 5. As regards tumour management outcomes, 40% of cases were still on treatment, 2.9% received radiotherapy. The survival rate was 60% versus 40% non-survived. The median overall survival duration was [10] months ranged between (5 and 53) months. See Table 6. After treatment by 1st line treatment AFP showed no statistically significant change in AFP from diagnosis time to time after 1st treatment line $p=0.14$. Table 7. The table illustrated that there was a statistically significant higher median of AFP (158) level among cases treated with (Lenvatinib) versus [5] in group treated with (Atezozolimab & bevacizumab) with $p=0.023$. On the other hand, there was no statistically significant difference in PFS level, and overall survival duration between two types of treatment in the 1st line with $p\text{-value} > 0.05$. see Table 8. The table illustrated that there was a statistically significant higher median of overall survival duration among cases with negative HBV 13.5 m versus 6 months among cases with positive HBV $p=0.006$. On the other hand, there was no statistically significant difference in overall survival duration between sex, stage of disease, portal vein thrombosis, and way of diagnosis $p\text{-value} > 0.05$ Table 9. The table illustrated that there was no statistically significant difference in overall survival duration between RFA, and TARE groups $p\text{-value} > 0.05$ Table [10]. Kaplan -Meier test illustrated that exactly 50% of the patients in this treatment group survived longer than 16 months, and the other 50% survived less than 16 months. 95% Confidence Interval (CI): 10.913 to 21.087. table [11]. This indicates that if this treatment were given to the wider population, we are 95% confident the true median survival would fall between roughly 11 and 21 months. as regards mean survival duration it was 21.8 months ranged between 14.8- and 28.8-months Figure 1. The overall survival duration showed a statistically significant negative correlation with each of total bilirubin level and child score in addition to positive correlation with PFS level after 1st line treatment ($p=0.047$, 0.049, and <0.001 respectively) Table 12.

Which indicated an increase in total bilirubin level and child score and decrease in PFS level will associate with decrease in overall survival duration among cases. On the other hand, there was no statistically significant correlation with $p\text{-value} > 0.05$ between overall survival duration and other variables Figure 2,3,4.

Table 1: Description of demographic and clinical characteristic among study group.

Variables	Number (n=35)	
	Mean $\pm$ SD	Median (Range)
Age (years)	69.5 $\pm$ 8.5	71(58-90)
Sex	No.	%
Male	31	88.6%
Female	4	11.4%
Stage of disease		
Stage I	1	2.9%
Stage II	2	5.7%
Stage III	22	62.9%
Stage IV	10	28.6%
Portal vein thrombosis		
No	21	60%
Yes	14	40%
HBV		
Negative	26	74.3%
Positive	9	25.7%
HCV		
Negative	29	82.9%
Positive	6	17.1%
Way of diagnosis		
Radiologically	28	80%
Biopsy	7	20%
Lines of treatments		
1 st line	31	88.6%
2 nd line	9	25.7%
3 rd line	3	8.6%
4 th line	2	5.7%
5 th line	1	2.6%
Laboratory investigation		
AFP at diagnosis	2028.4 $\pm$ 4911.2	173(4.4-24210)
Albumin	33.7 $\pm$ 7.06	33.3(17-45)
INR	1.22 $\pm$ 0.17	1.2(1-1.7)
T. Bilirubin	26.02 $\pm$ 39.5	14.7(3.2-228)
Child score	6.17 $\pm$ 1.24	6(5-10)

Table 2: Description of cases assessment at 1st line treatment among study group.

Variables	Number (n=35)	
	No.	%
1st line of treatment		
No	4	11.4%
Atezozolimzb & lenvatinib	1	2.9%
Atezozolimab & bevacizumab	15	42.9%
Lenvatinib	15	42.9%
laboratory investigation after treatment	Mean $\pm$ SD	Median (Range)
PFS	8.66 $\pm$ 9.7	5(1-48)
AFP	1171.9 $\pm$ 3512.4	15.5(0-17000)
Side effects		
No	24	68.6%
Vomiting	1	2.9%
Fatigue	9	25.7%
Skin rashes	1	2.9%

Table 3: Description of cases assessment at 2nd line treatment among study group.

Variables	Number	
	(n=9)	
	No.	%
2nd line of treatment		
Lenvatinib	3	33.3%
Cabozantinib	4	44.4%
Sorafenib	1	11.1%
Ramucirumab	1	11.1%
laboratory investigation after treatment	Mean $\pm$ SD	Median (Range)
PFS	3.6 $\pm$ 2.5	3.5(1-9)
AFP	5715.9 $\pm$ 17828.6	22(2-59412)
Side effects		
No	5	55.6%
Skin rashes	3	33.3%
Diarrhea	1	11.1%

Table 4: Description of cases assessment at 3rd, 4th, and 5th lines of treatment among study group.

Variables	Number	
	(n=3)	
	No.	%
3rd line of treatment	(n=3)	
Sorafenib	1	33.3%
Regorafenib	2	66.7%
4th line of treatment	(n=2)	
Regorafenib	1	50%
Ramucirumab	1	50%
5th line of treatment	(n=1)	
Atezolizumab & bevacizumab	1	100%
PFS	Mean $\pm$ SD	Median (Range)
After 3 rd line treatment	3 $\pm$ 0	3(3-3)
After 4 th line treatment	2 $\pm$ 1.4	2(1-2)
After 5 th line treatment	8 $\pm$ 0	8(8-8)

Table 5: Description of different way of tumor management among study group.

Variables	Number	
	(n=35)	
	No	%
RFA		
No	32	91.4%
Yes	3	8.6%
TARE		
No	32	91.4%
Yes	3	8.6%
TACE		
No	34	97.1%
Yes	1	2.9%

Table 6: Description of final outcomes among study group.

Variables	Number (n=35)	
	Mean $\pm$ SD	Median (Range)
Overall survival (m)	14.51 $\pm$ 11.7	10(5-53)
Still on treatment	No.	%
No	21	60%
Yes	14	40%
Radiotherapy		
No	34	97.1%
Yes	1	2.9%
Survival rate		
Non-survived	14	40%
Survived	21	60%

Table 7: Comparisons of AFP at diagnosis time and after treatments in 1st line of treatments among study group.

AFP	Median (Range)	p-value
At diagnosis	173(4.4-24210)	0.14
After 1 st line treatment	15.5(0-17000)	

Table 8: Comparisons between treatments in 1st line of treatments as regards PFS, AFP and overall survival duration among study group.

Variables	1 st line treatment				P-value
	Atezozolimab & bevacizumab (n=15)		Lenvatinib (N=14)		
	Median	Range	Median	Range	
PFS	5	1-48	4.5	1-16	0.41
AFP	5	0-3200	158	0-17000	0.023*
Overall survival	13	2-53	11	5-43	0.97

Table 9: Comparison of overall survival duration in different clinical data among study group.

Variables	Overall survival (m)		p-value
	Median	(Range)	
Sex			
Male	10	2-53	0.71
Female	13	6-27	
Stage of disease			
Stage I	10	10-10	0.97
Stage II	13	8-18	
Stage III	10	4-53	
Stage IV	12.5	2-43	
Portal vein thrombosis			
No	10	3-53	0.83
Yes	12.5	2-43	
HBV			
Negative	13.5	5-43	0.006*
Positive	6	2-53	
HCV			
Negative	10	2-53	0.95
Positive	11	5-18	
Way of diagnosis			
Radiologically	10	2-53	0.95
Biopsy	13	3-23	

Table 10: Comparison of overall survival duration in different way of tumor management among study group.

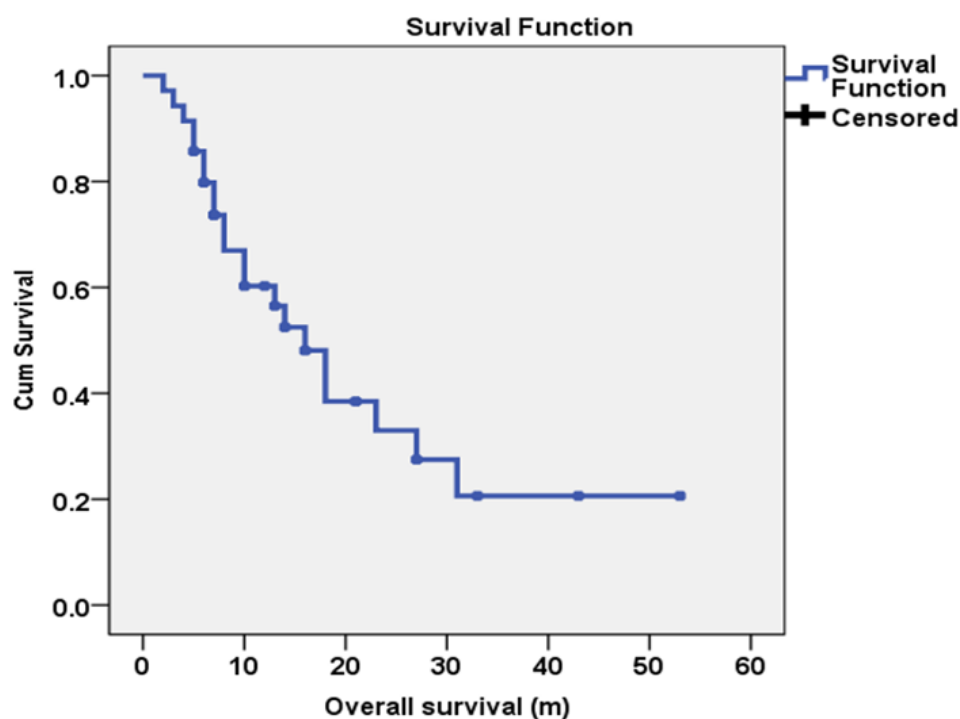
Variables	Overall survival (m)		p-value
	Median	Range	
RFA			
No	11	2-53	0.72
Yes	10	10-18	
TARE			
No	12.5	2-53	0.19
Yes	7	5-8	

Table 11: Kaplan -Meier test overall surviving duration among study group.

	Estimate	SE	95% Confidence Interval	
			Lower Bound	Upper Bound
Mean	21.821	3.570	14.825	28.817
Median	16.000	2.596	10.913	21.087

Table 12: Correlation between overall survival duration with clinical and laboratory data among cases.

Variables	Overall survival duration	
	r	P-value
Age (years)	0.19	0.25
AFP at diagnosis	-0.07	0.70
Albumin	0.07	0.67
INR	-0.08	0.63
T. Bilirubin	-0.34	0.047*
Child score	-0.33	0.049*
AFP after 1 st line treatment	0.11	0.55
PFS level after 1 st line treatment	0.73	0.001*

**Figure 1:** Overall survival according to BCLC stage in patients with hepatocellular carcinoma. Kaplan–Meier curves demonstrating overall survival among patients with BCLC stage B and stage C disease.

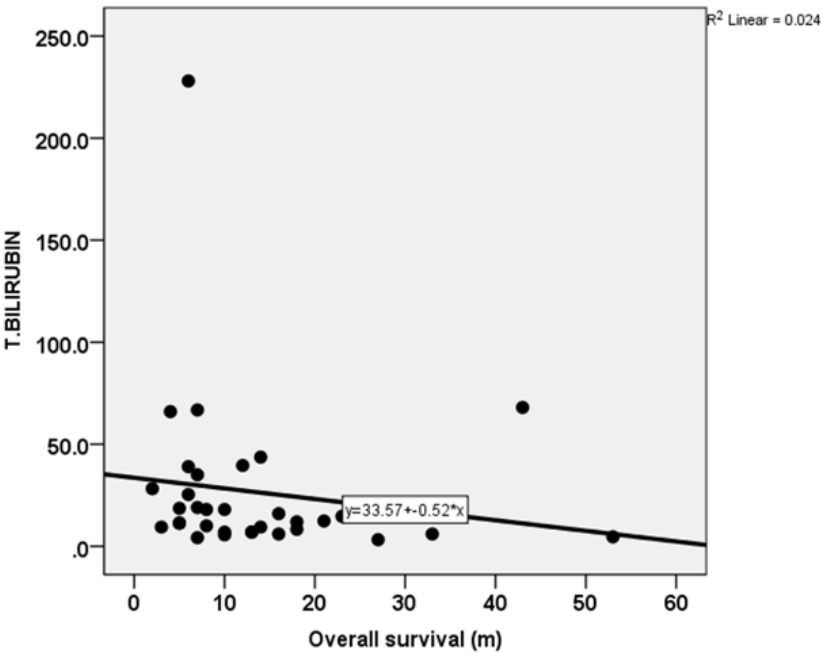


Figure 2: Correlation between overall survival duration with total bilirubin.

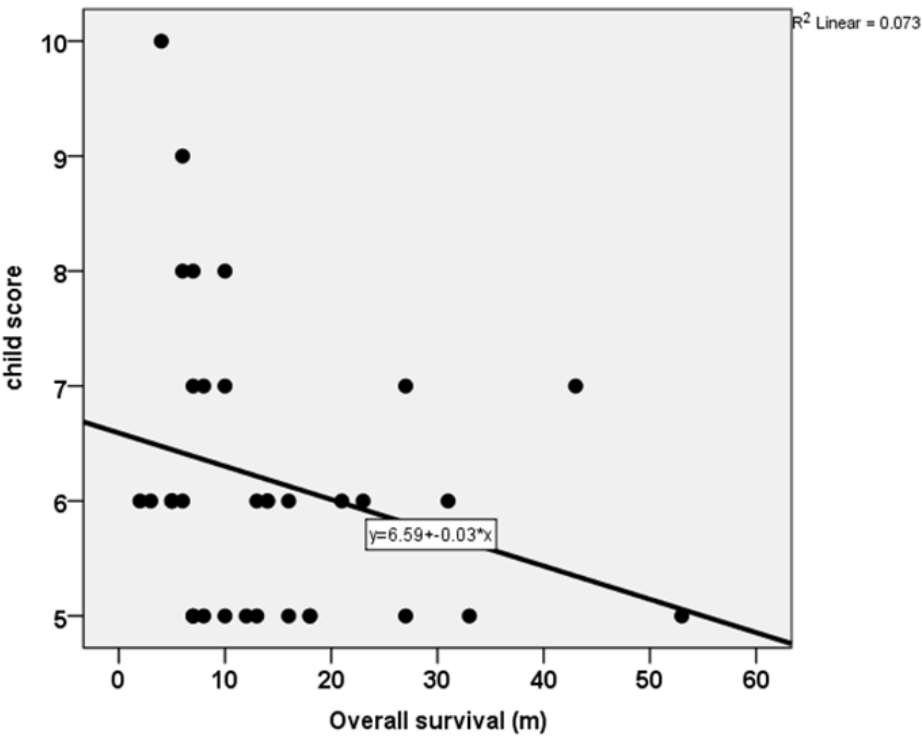


Figure 3: Correlation between overall survival duration with child score.

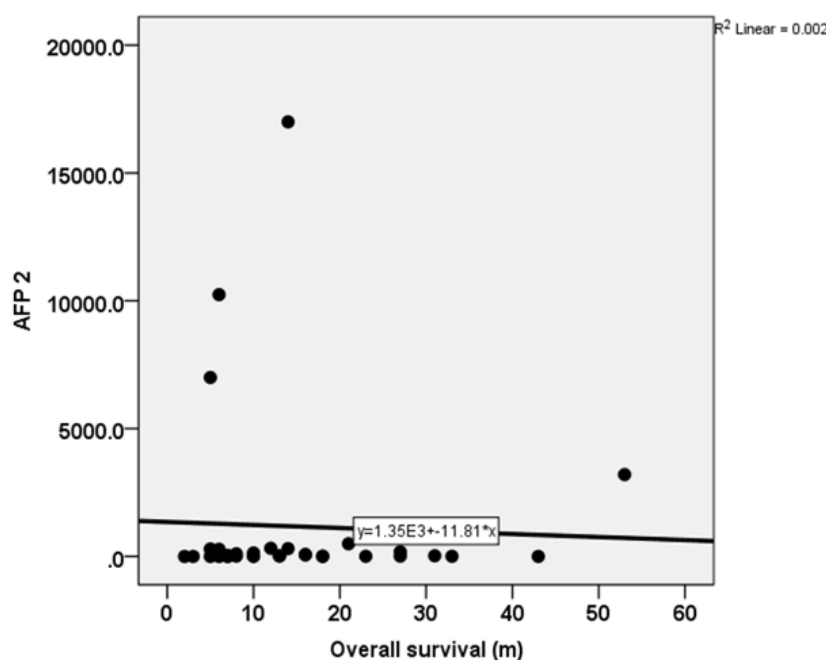


Figure 4: Correlation between overall survival duration with AFP.

6. Discussion

The present study evaluated the clinical characteristics, treatment patterns, and outcomes of patients with intermediate or advanced hepatocellular carcinoma (HCC) treated in a real-world setting. The findings provide insight into the characteristics of patients encountered in routine practice and allow comparison with outcomes reported in major randomized clinical trials.

The mean age of the study population was 69.5 ± 8.5 years, and men constituted the majority of the cohort (88.6% males versus 11.4% females). This sex distribution is consistent with the established epidemiological pattern of HCC, in which male sex is recognized as an important risk factor. Most patients presented with advanced disease: 62.9% had stage III disease and 28.6% had stage IV disease. In addition, 40% had portal vein thrombosis, indicating a considerable tumour burden and an unfavourable disease characteristic. Portal venous invasion may compromise hepatic blood flow and facilitate intrahepatic tumour dissemination, and it has consequently been associated with poorer survival. The advanced presentation observed in our cohort is relevant when comparing our findings with randomized trials, which commonly enroll carefully selected patients with better performance status and relatively preserved hepatic function.

With respect to underlying etiology, 25.7% of patients had a history of HBV infection, whereas 17.1% had HCV infection. Viral hepatitis continues to represent an important etiological factor in HCC. Chronic HBV and HCV infection can contribute to malignant transformation through persistent inflammation, repeated hepatocellular injury, fibrosis, and progression to cirrhosis. HBV may additionally contribute through direct viral mechanisms, including integration of viral DNA into the host genome. Thus, viral hepatitis represented a clinically relevant component of the underlying liver disease in our study population.

Radiological assessment was the basis for diagnosis in 80% of patients. This finding is consistent with current clinical practice, as HCC can often be diagnosed without tissue confirmation when typical imaging characteristics are present in an appropriate clinical setting. In patients with cirrhosis or chronic viral hepatitis, characteristic enhancement during the arterial phase followed by washout during the portal venous or delayed phase can provide sufficient evidence for diagnosis. The high proportion of radiologically diagnosed cases in our cohort therefore reflects the practical application of contemporary diagnostic strategies.

The laboratory profile indicated a substantial burden of both tumour activity and hepatic dysfunction. The median AFP concentration at diagnosis was 173, while the median albumin level was 33.3, median INR was 1.2, and median total bilirubin was 14.7. The median Child-Pugh score was 6. Although a proportion of patients maintained relatively preserved liver function, these findings suggest clinically meaningful impairment in others. Hepatic reserve is particularly important in advanced HCC because treatment tolerance and prognosis depend not only on control of tumour progression but also on the ability of the liver to maintain its function. Consequently, worsening hepatic function can contribute to mortality independently of radiological progression.

The prognostic importance of hepatic reserve has also been demonstrated in analyses from the REFLECT study by Huynh J et al. Among patients receiving lenvatinib, deterioration to Child-Pugh B was associated with substantially poorer outcomes than maintenance of Child-Pugh A status. Median PFS from the landmark assessment was 3.7 months in patients with Child-Pugh B compared with 6.5 months in those with Child-Pugh A, whereas median OS was 6.8 versus 13.3 months, respectively [16]. These observations are consistent with our findings, in which indicators of impaired hepatic function, particularly bilirubin and Child-Pugh score, were associated with shorter survival.

Most patients in our cohort received systemic therapy, with 88.6% receiving first-line treatment. A smaller proportion subsequently received additional lines of treatment: 25.7% received second-line therapy, 8.6% received third-line therapy, and only small proportions continued to fourth-line or later treatment. These findings illustrate the importance of treatment sequencing in advanced HCC. Nevertheless, progression following first-line therapy does not necessarily lead to another treatment opportunity. Declining performance status, deterioration in hepatic function, or rapidly progressive disease may prevent patients from receiving subsequent systemic therapy.

7. Evolution of Systemic Treatment in Advanced HCC

Sorafenib represented the first systemic treatment to establish a survival benefit in advanced HCC. In the SHARP trial reported by Llovet JM et al., sorafenib improved median OS compared with placebo, 10.7 versus 7.9 months, and increased the median time to radiological progression, 5.5 versus 2.8 months [6]. These results established sorafenib as the principal systemic treatment for advanced HCC for an extended period.

The therapeutic options subsequently expanded with the introduction of lenvatinib. The phase III REFLECT trial conducted by Kudo M et al. demonstrated that lenvatinib was non-inferior to sorafenib with respect to OS, with median OS of 13.6 and 12.3 months, respectively [7]. Lenvatinib also produced a longer median PFS, approximately 7.4 versus 3.7 months, together with a higher objective response rate. These findings established lenvatinib as an effective first-line option for patients with unresectable HCC.

More recently, immunotherapy-based combinations have substantially altered the first-line treatment landscape. In the IMbrave150 trial, Cheng AL, Qin S, Ikeda M, et al. demonstrated improved outcomes with atezolizumab plus bevacizumab compared with sorafenib. In the updated analysis, median OS was 19.2 months with atezolizumab plus bevacizumab compared with 13.4 months with sorafenib, while median PFS was 6.9 versus 4.3 months, respectively [9]. These results established atezolizumab plus bevacizumab as an important preferred first-line treatment for appropriately selected patients with unresectable HCC.

Another major immunotherapy-based approach was evaluated in the HIMALAYA trial by Kelley RK, Rimassa L, Cheng AL, et al. Treatment with tremelimumab plus durvalumab resulted in a median OS of 16.4 months, compared with 13.8 months with sorafenib [17]. These results provided further evidence supporting the role of immunotherapy-based strategies in advanced HCC.

8. Comparison between Atezolizumab Plus Bevacizumab and Lenvatinib

A notable finding in the present study was the statistically significant difference in baseline AFP between the two first-line treatment groups. Patients treated with lenvatinib had a median AFP level of 158, compared with 5 in patients receiving atezolizumab plus bevacizumab ($p=0.023$). This baseline difference is clinically relevant because AFP may reflect tumor burden and aggressive tumor characteristics and is widely used as a prognostic biomarker

in HCC.

The higher AFP concentration among patients receiving lenvatinib indicates that the treatment groups were not fully comparable at baseline. Consequently, comparisons of subsequent PFS and OS between the two treatment groups should be interpreted with caution. Differences in tumor biology or disease burden between treatment groups may influence survival independently of the treatment administered.

Despite the baseline AFP imbalance, no statistically significant difference in PFS was identified between the two treatment groups. Median PFS was 5 months for atezolizumab plus bevacizumab and 4.5 months for lenvatinib ($p=0.41$). Although the numerical difference favored atezolizumab plus bevacizumab by approximately 0.5 months, this difference did not reach statistical significance.

A similar finding was observed for OS. Median OS was 13 months in the atezolizumab plus bevacizumab group and 11 months in the lenvatinib group ($p=0.97$). Therefore, our study did not demonstrate a statistically significant difference in survival between the two first-line regimens.

The survival outcomes in our cohort were generally lower than those reported in the corresponding pivotal randomized trials. Patients receiving lenvatinib had a median PFS of 4.5 months, compared with 7.4 months in REFLECT, while median OS was 11 months, compared with 13.6 months in that trial [7]. Similarly, the median PFS of 5 months and OS of 13 months observed with atezolizumab plus bevacizumab were lower than the 6.9-month PFS and 19.2-month OS reported in the updated IMbrave150 analysis [9].

Several characteristics of our population may account for these differences. First, our cohort represented a real-world population in which a large proportion had advanced-stage disease and 40% had portal vein thrombosis. Second, laboratory parameters suggested a degree of hepatic dysfunction, as reflected by albumin and Child-Pugh scores. Third, the cohort included patients with both HBV and HCV infection and potentially diverse underlying tumor biology. Finally, patients enrolled in randomized controlled trials generally need to satisfy stringent eligibility requirements and consequently tend to have better performance status and hepatic reserve than patients treated in routine clinical practice.

The absence of a statistically significant difference between atezolizumab plus bevacizumab and lenvatinib should therefore not be interpreted as demonstrating equivalent efficacy of the two treatments across all patient populations. The relatively small cohort and the significant baseline difference in AFP limit the reliability of direct treatment comparisons. Contemporary comparative and meta-analytic evidence has generally favored atezolizumab plus bevacizumab over tyrosine kinase inhibitors in appropriately selected patients, although the magnitude of this benefit may differ according to disease etiology and baseline clinical characteristics [18].

9. HBV Status and Overall Survival

HBV status was another important variable associated with survival in our study. Patients without HBV infection had a median OS

of 13.5 months, compared with 6 months among HBV-positive patients ($p=0.006$). The magnitude of this difference suggests that HBV status may have an important prognostic association in this cohort.

Nevertheless, the relationship between viral etiology and outcomes in HCC is complex and remains incompletely defined. A multicenter study by Rodolfo Sacco et al. involving 313 patients treated with lenvatinib reported shorter survival among patients with viral compared with nonviral disease. Median OS was 15 months in the viral group versus 21 months in the nonviral group, while median PFS was 6 versus 9 months, respectively [19]. These findings are directionally consistent with the association identified in our population.

Conversely, other real-world studies have not demonstrated a significant negative effect of viral etiology among patients treated with atezolizumab plus bevacizumab. In a real-world study by Timothy J. Brown et al. involving 429 patients who received first-line atezolizumab plus bevacizumab, HCC etiology was not significantly associated with OS [20]. Similarly, Rossari F et al. [20] in a multicentre real-world analysis of 885 patients treated with atezolizumab plus bevacizumab, reported comparable median OS between viral and nonviral HCC, 15.9 versus 16.3 months, respectively. Time to progression was also similar, at 8.3 versus 7.2 months [21].

Accordingly, the shorter OS observed among HBV-positive patients in our cohort should be regarded as an association rather than evidence that HBV infection itself reduces the effectiveness of systemic therapy. Other factors may have contributed to this finding, including tumour burden, portal vein invasion, AFP concentration, hepatic reserve, HBV activity, antiviral therapy, performance status, and the availability or use of subsequent treatment.

The discrepancy between our results and some contemporary real-world studies is noteworthy. The difference may be related to the small size of our cohort and variation in the distribution of other prognostic factors. A larger cohort with multivariable adjustment would be required to determine whether HBV status independently predicts OS after accounting for other clinically relevant variables.

10. Predictors of Overall Survival

Our analysis also identified significant relationships between OS and selected measures of hepatic function. OS showed a statistically significant negative correlation with total bilirubin and Child-Pugh score, with p -values of 0.047 and 0.049, respectively. In contrast, a strong positive correlation was observed between OS and PFS following first-line treatment ($p<0.001$).

These findings emphasize the close interaction between hepatic reserve and tumor control in advanced HCC. The relationship between bilirubin and survival is biologically plausible because bilirubin is an important marker of hepatic dysfunction. Elevated bilirubin may occur in the setting of worsening cirrhosis, portal hypertension, extensive tumor involvement, biliary obstruction, or hepatic decompensation. Patients with impaired liver function may tolerate systemic treatment less effectively and may also be

exposed to a higher risk of death resulting from hepatic failure in addition to tumor progression.

The association between Child-Pugh score and OS provides further evidence of the prognostic relevance of hepatic reserve. An increasing Child-Pugh score reflects worsening hepatic function, incorporating parameters such as bilirubin, albumin, coagulation status, ascites, and encephalopathy. Our findings are in agreement with the REFLECT analysis showing substantially poorer outcomes among patients who deteriorated from Child-Pugh A to Child-Pugh B [16].

The strongest statistical association in our analysis was observed between PFS after first-line therapy and OS, with $p<0.001$. Patients who remained free of progression for a longer period tended to have longer overall survival. Longer disease control may delay tumor-related deterioration, preserve hepatic function and performance status, and increase the likelihood that a patient remains eligible for additional systemic treatment.

Treatment sequencing may also contribute to the observed relationship between PFS and OS. In our cohort, 25.7% of patients received second-line treatment, while smaller numbers proceeded to third-line and subsequent therapies. Patients with early disease progression may deteriorate rapidly and consequently lose the opportunity to receive further treatment. In contrast, patients who maintain disease control may remain clinically fit enough to receive additional lines of therapy. Thus, prolonged PFS may reflect both favorable tumor biology and better preservation of overall clinical condition.

No statistically significant association was detected between OS and the other variables examined. These negative findings should, however, be interpreted in the context of the small study population of 35 patients. The limited sample size reduces statistical power and may prevent detection of moderate associations.

11. Kaplan-Meier Analysis and Overall Survival

Kaplan-Meier analysis demonstrated a median OS of 16 months in the analyzed treatment group, with a 95% confidence interval of 10.913–21.087 months. This indicates that approximately one-half of the patients remained alive beyond 16 months, whereas the remaining patients experienced the event before that point.

The mean survival duration was 21.8 months, with a range/estimated interval of 14.8–28.8 months. In survival analyses, the median is generally considered a more appropriate primary summary measure because survival distributions are frequently skewed and may contain censored observations. Therefore, the median OS of 16 months should be regarded as the principal estimate, with the mean value providing additional descriptive information.

The median OS of 16 months in our analysis falls within the range reported in contemporary systemic-treatment studies. It is comparable to the 16.4-month OS reported for tremelimumab plus durvalumab in HIMALAYA and is longer than the historical survival reported with sorafenib in SHARP, although it remains below the 19.2-month OS reported for atezolizumab plus bevacizumab in the updated IMbrave150 analysis [6,9,17]. Direct comparisons

should nevertheless be made cautiously because our cohort represents a small real-world population with different baseline characteristics and treatment sequences from those included in randomized clinical trials.

12. Second-Line Treatment

Sequential therapy represented an important component of treatment in our population. 25.7% of patients progressed to second-line treatment. Among these patients, 44.4% received cabozantinib and 33.3% received lenvatinib. The median PFS following second-line therapy was 3.5 months, with a range of 1–9 months.

The PFS observed following second-line treatment was broadly comparable with results reported in clinical trials evaluating systemic therapies after prior treatment. In the CELESTIAL trial, Abou-Alfa GK, Meyer T, Cheng AL, et al. demonstrated a survival benefit with cabozantinib compared with placebo in patients with previously treated advanced HCC. Median OS was 10.2 versus 8.0 months, while median PFS was 5.2 versus 1.9 months, respectively [22]. The somewhat shorter PFS observed in our cohort may be attributable to the small number of patients and the less selected clinical characteristics of real-world populations.

Regorafenib is another established treatment option for selected patients following progression on sorafenib. In the RESORCE trial by Bruix J, Qin S, Merle P, et al., regorafenib resulted in a median OS of 10.6 versus 7.8 months and median PFS of 3.1 versus 1.5 months compared with placebo [23]. These findings demonstrate that appropriately selected patients may derive additional disease control and survival benefit from subsequent systemic therapy.

Only 25.7% of patients in our study proceeded to second-line therapy. This observation has important clinical implications because progression of advanced HCC may occur together with deterioration in hepatic function and performance status. Such deterioration can make patients unsuitable for additional systemic therapy. Consequently, the opportunity to receive subsequent treatment may itself contribute substantially to long-term outcomes.

13. Treatment Related Adverse Effects

Treatment-related adverse events were documented in 44.4% of patients receiving second-line treatment. The most frequently reported toxicity was skin rash, occurring in 33.3%, while diarrhea was reported in 11.1%.

The adverse-event pattern observed in our cohort is compatible with the known toxicity profiles of tyrosine kinase inhibitors used in advanced HCC. In CELESTIAL, cabozantinib was associated with grade 3 or 4 adverse events in 68% of patients, with palmar-plantar erythrodysesthesia, hypertension, increased AST, fatigue, and diarrhea among the principal toxicities [22]. In REFLECT, frequently reported adverse events associated with lenvatinib included hypertension, diarrhea, reduced appetite, and weight loss [7].

The apparently lower frequency of adverse events in our cohort should be interpreted cautiously. Only a small number of patients received second-line treatment, and the retrospective design may

have resulted in incomplete documentation of treatment-related toxicity. Therefore, toxicity rates from our study should not be directly compared with those obtained from prospective randomized trials.

14. Treatment Continuation and Overall Survival

At the time of assessment, 40% of patients remained on treatment, whereas 2.9% had received radiotherapy. Overall, 60% of patients were alive and 40% had died. The overall median OS for the cohort was 10 months, with survival ranging from 5 to 53 months.

The median OS of 10 months in the overall cohort was lower than that reported in several contemporary first-line studies, including REFLECT and IMbrave150. However, it was close to the historical median OS of 10.7 months reported with sorafenib in SHARP [6,7,9]. This observation should not be interpreted as suggesting that modern systemic treatments provide no benefit beyond sorafenib. Rather, it is likely to reflect differences between our real-world population and the highly selected populations enrolled in pivotal trials. In particular, advanced-stage disease, portal vein thrombosis, hepatic dysfunction, viral hepatitis, and differences in subsequent treatment may all have contributed to the observed survival.

The broad survival range of 5–53 months further demonstrates the clinical heterogeneity of advanced HCC. Some patients can maintain disease control for prolonged periods, whereas others experience rapid progression and death. These differences emphasize the importance of individualized treatment decisions that take into account tumor burden, hepatic reserve, performance status, disease etiology, and anticipated treatment tolerance.

15. Limitations

Several limitations should be considered when interpreting these findings.

First, the study involved only 35 patients, which substantially limits statistical power and reduces the precision of the estimated survival outcomes.

Second, the observational design introduces the possibility of selection bias and residual confounding. Treatment allocation was not randomized, and the statistically significant difference in baseline AFP indicates that the two treatment groups were not fully balanced.

Third, relatively few patients received second-line or later-line systemic therapy. Therefore, the study cannot provide definitive conclusions regarding the comparative efficacy or toxicity of individual subsequent-line treatments.

Fourth, OS may have been affected by therapies administered after first-line treatment, including second- and later-line systemic therapy and radiotherapy. Consequently, overall survival cannot be attributed solely to the initial treatment received.

Finally, although HBV status demonstrated a statistically significant association with OS, the current analysis does not establish that HBV status represents an independent prognostic factor. Multivariable analysis in a larger cohort would be required to determine

whether this association persists after adjustment for other potentially influential clinical and tumor-related variables.

16. Conclusion

In conclusion, our findings demonstrate that outcomes among patients with advanced HCC treated in routine clinical practice may differ from those reported in randomized controlled trials. Differences in disease stage, portal vein involvement, AFP concentration, hepatic function, viral etiology, and access to subsequent treatment may all contribute to this variation.

The significant association between HBV status and OS observed in our cohort warrants further investigation but should not be interpreted as evidence of an independent effect in the absence of multivariable analysis. Similarly, the lack of a statistically significant difference between atezolizumab plus bevacizumab and lenvatinib should be interpreted in light of the small sample size and baseline AFP imbalance.

Larger prospective studies and well-designed multicenter real-world analyses are needed to clarify the independent prognostic significance of HBV infection, hepatic function, AFP, and treatment-related disease control. Such studies may also help identify the clinical and biological characteristics that can guide selection of the most appropriate systemic treatment strategy for individual patients with advanced HCC.

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