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Association between albumin-bilirubin (ALBI) score and Child Pugh (CP) score in Lenvatinib-treated South Indian hepatocellular carcinoma patients

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Abstract:

Background: In advanced hepatocellular carcinoma (HCC), baseline liver function is crucial for predicting survival, therapeutic effectiveness, and safety outcomes. A proven, objective indicator of hepatic reserve, the albumin–bilirubin (ALBI) score may be a better indicator of prognosis for patients undergoing systemic therapy.

Objective: This study examines the effects of baseline Child Pugh score and ALBI grade on patients with hepatocellular cancer who were treated with lenvatinib.

Methods: All patients who received lenvatinib as a first- or second-line therapy for advanced HCC at our hospital between 2020 and 2024 were included in this retrospective study. The Child-Pugh score and ALBI grade were used to classify baseline liver function. The objective response rate (mRECIST), time to treatment failure (TTF), progression-free survival (PFS), overall survival (OS), and treatment discontinuation due to adverse events (AEs) were the primary outcomes evaluated. The patients were divided into four groups: Child-Pugh A5/ALBI 1, Child-Pugh A5/ALBI 2, Child-Pugh A6, and Child-Pugh ≥ 7 . To identify determinants of response and discontinuation, univariate and multivariate analyses were conducted.

Results: The cohort's median overall survival (OS) and progression-free survival (PFS) were 27.4 months and 13.5 months, respectively. The OS (38.4 vs. 20.4 months) and PFS (15.3 vs. 11.5 months) of patients with ALBI grade 1 were considerably longer. Group 4 had the lowest survival rate, while Group 1 had the highest. The most frequent adverse events were fatigue (30%) and anorexia (22%). Disease progression was independently predicted by higher initial dosages and extrahepatic distribution.

Conclusion: The prognosis of HCC patients on lenvatinib was effectively stratified by baseline ALBI grade. The higher survival and tolerability of patients with preserved liver function (ALBI grade 1) suggest ALBI as a crucial adjunct to the Child-Pugh score in treatment planning.

Keywords: Hepatocellular carcinoma, ALBI grade, Child Pugh score, Lenvatinib, liver function, real-world evidence

INTRODUCTION:

Globally, liver cancer, particularly hepatocellular carcinoma (HCC), ranks third in cancer-related mortality and sixth in terms of incidence¹. HCC is a formidable malignancy, frequently diagnosed at advanced stages, underscoring the critical need for effective prognostic indicators to guide therapeutic strategies². In India, it ranks 11th in cancer incidence and 8th in mortality, with 38,703 new cases and 36,953 deaths annually^{3,4}. In South India, MASLD has been identified as a significant etiological factor for HCC, surpassing the viral causes. Notably, 14.5% of biopsy samples

revealed steatohepatitis coexisting with HCC, highlighting the metabolic basis of malignancy in this region. Musunuri et al⁵ reported that over half of HCC cases in a tertiary-care cohort from coastal South India were cryptogenic/NAFLD-related, with many patients presenting at advanced BCLC stages and only a minority detected through surveillance. Similarly, the results from a large multicentre Kerala HCC survey conducted by Koshy et al⁶ showed that 44% of HCC patients had metabolic syndrome or NAFLD, with a high prevalence of diabetes (64%) and hypertension (38%), and the majority of them presented at stages where curative therapy was not practical. These convergent datasets show that MASLD is a fast-increasing oncogenic driver in South India, highlighting the need for earlier surveillance mechanisms and improved metabolic risk classification. There is an evolving landscape involving a multi-disciplinary team in the treatment options available for various stages of liver cancer⁷. Targeted multi-kinase inhibitor therapy and immune checkpoint inhibitors are the systemic therapies for unresectable HCC. The paradigm for treating HCC has changed with the introduction of targeted treatments like lenvatinib⁸⁻¹⁰.

Lenvatinib, a multi-potent tyrosine kinase inhibitor that targets the vascular endothelial growth factor receptors 1-3, fibroblast growth factor receptor 1-4, platelet-derived growth factor receptor α , RET, and KIT, has gained popularity over sorafenib after the REFLECT trial. The study showed lenvatinib had a tolerable safety profile, non-inferior overall survival, and a greater response rate in comparison to sorafenib^{10,11}.

The recent ASCO 2024 guidelines suggest the immune checkpoint inhibitors (Atezolizumab–bevacizumab/Durvalumab–tremelimumab) for Child-Pugh A patients with a good performance score of 0-1. Lenvatinib remains a vital option when the above therapies are contraindicated¹². Real-world studies suggest that lenvatinib has demonstrated improved overall survival and a better safety profile in the HCC population. The response achieved with lenvatinib is, however, significantly influenced by the patients' baseline liver function. Deteriorated liver function not only limits the treatment options but can also increase the risk of adverse events and alter the well-being of the patient and his/her family¹³⁻¹⁵.

The Child–Pugh scoring system is one of the traditional methods used to assess liver function and includes subjective parameters such as hepatic encephalopathy and

ascites grading. However, considerable interobserver variability has been reported among clinicians, limiting its reproducibility. Due to this lack of objectivity and specificity, newer grading systems based on quantitative parameters—such as the albumin–bilirubin (ALBI) grade—were developed to provide a more standardized assessment of liver function^{16,17}.

The ALBI grade, a recently developed scoring system based on two objective biochemical parameters—serum albumin and bilirubin—is used for liver function assessment in patients with hepatic diseases, particularly HCC. It has emerged as a promising tool for risk stratification and prognostication in various liver diseases, including HCC¹⁸. Several studies have demonstrated the significance of the ALBI grade in predicting overall survival, guiding treatment strategies, and determining the toxicity profile in patients with HCC¹⁸. Studies from India consistently demonstrate that the ALBI grade offers better predictive discrimination than the conventional Child-Pugh score, especially for patients who are categorized as Child-Pugh A¹⁹. A real-world tertiary cancer center cohort presented at ASCO confirmed ALBI's stronger prognostic value in advanced HCC under systemic therapy²⁰, while a retrospective cohort from Eastern India showed that ALBI more accurately stratified survival and liver-related complications than Child–Pugh¹⁹. These results are consistent with larger analyses conducted in Asia and South Asia, where ALBI consistently performs better than Child-Pugh in resection, trans arterial chemoembolization (TACE), and systemic-therapy settings²¹. Our study endeavours to evaluate the prognostic utility of the albumin–bilirubin score in a South Indian cohort of HCC patients undergoing lenvatinib treatment, addressing a critical regional gap in current literature.

METHODS:

2.1 Study design: The medical records of 502 consecutive patients diagnosed with advanced HCC and treated with lenvatinib as first /second line treatment between 2019 to 2024 at our institution were reviewed. This retrospective single-centre study was approved by the institutional ethics committee of Amrita School of Medicine, ECASM-AIMS-2021-293 on 15-06-2021, and was conducted as per the principles of the Declaration of Helsinki and guidelines of the Indian Council of Medical Research.

2.2 Inclusion criteria: Unresectable adult HCC patients substantiated by radiographic or histological findings, Barcelona Clinic Liver Cancer (BCLC) stage B or C; Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1; Child-Pugh score received lenvatinib as 1st or 2nd line therapy, were included.

Exclusion criteria: Patients were excluded if they had incomplete patient data history and were not willing to take part in the study.

2.3 Lenvatinib treatment regimen: Lenvatinib (Lenvima ®, Eisai Co Ltd, Tokyo, Japan; or Lentykine ®, Intas Pharmaceuticals; or Lenvat ®, Natco Pharma Ltd; or Adlante ®, Adley formulations) was given orally to advanced HCC patients.

As per the Food and Drug Administration (FDA), the approved dose of oral lenvatinib was 8mg/day in patients with < 60kg body weight and 12 mg/day in patients with ≥ 60kg body weight. To prevent early cessation due to adverse events, a lower initial dose of lenvatinib is prescribed in patients with non-Child Pugh A illness, the elderly population, low body weight, pleural effusion, ascites, or gastrointestinal varices at risk of bleeding.

Any unacceptable or severe side effects or clinical progression resulted in discontinuation of lenvatinib. In accordance with the lenvatinib administration recommended, patients who experienced grade ≥ 3 severe adverse events or any unacceptable grade 2 related adverse events had their drug dosage either decreased or their therapy stopped. The National Cancer Institute Common Terminology criteria for adverse events (CTCAE), version 5.0, were used to evaluate the adverse events.

2.5 Treatment Protocol

Lenvatinib's effectiveness and safety in treating individuals with incurable HCC were assessed by grouping patients based on their Child-Pugh score and ALBI grade.

The patients were categorised into four groups:

Group 1: Child-Pugh score A5, ALBI grade 1

Group 2: Child-Pugh score A5, ALBI grade 2

Group 3: Child-Pugh score A6

Group 4: Child-Pugh score ≥ 7 (B or C)

2.6 Data Collection and Treatment Assessment

Clinical, demographic, and treatment-related data were retrospectively collected from electronic medical records. The collected parameters included patient age, sex, aetiology of liver disease, ECOG performance status, Child–Pugh classification, and details of systemic therapy received. Laboratory data at baseline and during treatment were extracted for biochemical and pharmacokinetic analysis.

ALBI score was calculated using serum albumin and bilirubin, thereby eliminating the subjective variables present in the Child–Pugh classification using the formula¹⁴:

$$\text{ALBI score} = (\log_{10} \text{bilirubin} \times 0.66) + (\text{albumin} \times -0.085)$$

where **bilirubin** is expressed in $\mu\text{mol/L}$ and **albumin** in g/L .

Patients were categorized into three grades based on the calculated score:

- **Grade 1:** ≤ -2.60
- **Grade 2:** > -2.60 to ≤ -1.39
- **Grade 3:** > -1.39

Treatment response was evaluated according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) using dynamic contrast-enhanced CT or MRI scans. Imaging assessments were performed at baseline and at regular follow-up intervals as per institutional protocol. Efficacy outcomes were assessed using key clinical endpoints, including overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and time to treatment failure (TTF) defined as time from initial administration to the time of treatment failure, which can be either due to treatment discontinuation or progression or death).

2.7 Statistical analysis

Statistical analysis was used using IBM SPSS version 20.00. Continuous variables are shown as medians (range). To test the statistical significance of the association of risk factors with dose reduction, progression, the Pearson chi-square test was applied. Multivariate logistic regression was done to examine the most significant risk factors

after adjusting for the confounding factors. To find the survival probability of overall survival and progression-free survival, Kaplan Meier analysis was computed, and also comparison was also determined using log log-rank test. A p-value < 0.05 was considered to be statistically significant.

Results

3.1 Baseline characteristics of the study population

A total of 502 patients with HCC were screened for eligibility between 2019 and 2024. Of these, 22 patients were excluded due to incomplete clinical data (n=10), unwillingness to participate in the study (n=5), or being second-opinion/one-time-visit cases (n=7). After applying the exclusion criteria, 480 patients were finally included in the analysis (Figure 1).

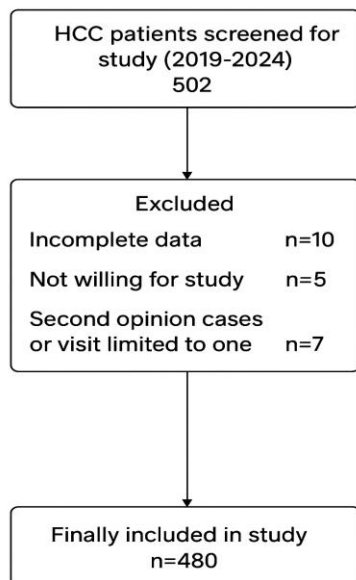


Figure 1. Flowchart showing the inclusion of patients

Table 1: Baseline characteristics

	Characteristics	Number	Percentage
Age	Mean age, years (range)	65.11 ± 8.9	(27-90)
Gender	Male	441	91.9
	Female	39	8.1
Aetiology	MASLD	176	37
	Alcohol	155	32.3
	Unknown	107	22.3
	Hepatitis B	30	6.25
	Hepatitis C	14	3
Lenvatinib starting dose	4mg OD	340	70.8
	8mg OD	126	26.3
	12mg OD	14	2.9
Comorbidities	Diabetes mellitus	339	70.6
	Hypertension	246	51.2
	Dyslipidaemia	65	13.5
Baseline liver function	Median Total bilirubin (mg/dl)	1.08	
	Median Serum albumin (g/dl)	3.67	
	Median INR (sec)	1.14	
Tumour markers	Median Alpha feto protein (ng/ml)	29.72	
	Median PIVKA (mAU/ml)	1090.11	
Child Pugh Score	A5	227	47.3
	A6	116	24.2
	B7	44	9.2

	B8	33	6.9
	B9	32	6.7
	C10	14	2.9
	C11	12	2.5
	C12	2	0.4
ALBI grade	1	154	32.1
	2	269	56
	3	57	11.9
BCLC score	A	149	31
	B	101	21
	C	230	47.9
Site of tumour	Right lobe	288	60
	Left lobe	76	16
	Both lobes	116	24
Number of liver lesions	1	177	36.9
	2	174	36.3
	3	63	13.1
	>3	66	13.8
Portal vein thrombosis	Main trunk	27	5.6
	Right anterior or posterior	56	11.7
	Right or left	27	5.6
	Segmental PV invasion	11	2.3
Extrahepatic spread	Lymph node	20	4.2
	Lung	16	3.3

	Bone	6	1.2
	Adrenal	2	0.4
	Brain	1	0.2
	Peritoneal	1	0.2
Cancer-directed therapies	Total patients undergone cancer-directed therapies	325	67.7
	MWA	93	29
	TACE	86	26.4
	RFA	55	17
	SBRT	43	13.2
	Liver resection	25	8
	Liver transplantation	14	4.3
	TARE	9	3

Abbreviations: MASLD - Metabolic Dysfunction-Associated Steatotic Liver Disease; INR - International Normalized Ratio; PIVKA-Protein Induced by Vitamin K Absence or antagonist-II; ALBI-Albumin-Bilirubin; BCLC - Barcelona Clinic Liver Cancer staging system; PV- portal vein; MWA-Microwave Ablation; TACE-Trans arterial chemoembolization; RFA-Radiofrequency ablation; SBRT-Stereotactic body radiation therapy; TARE-Trans arterial Radioembolization.

A summary of 480 eligible patients with baseline characteristics is presented in Table 1. There were 39 females and 441 males, with a mean age was 65.11 years. The most common aetiology was MASLD in 176 (37%) and alcohol in 155 (32.3%), followed by hepatitis B in 30 (6.2%) and hepatitis C in 14 (3%). The majority of the patients (340, 70.8%) were started with a lower dose of lenvatinib 4mg OD, irrespective of the FDA guidelines, followed by 126 (26.3%) with 8mg OD.

The most prevalent comorbidities were diabetes mellitus (70.6%) and hypertension (51.2%). The majority of patients belonged to Child Pugh Class A (71.5%), whereas

ALBI grade 2 (56%) was the most prevalent. Of the cohort, nearly half (47.9%) were in BCLC stage C. Single or double focal lesions were the most common (73.2%), and the right lobe accounted for 60% of the tumour involvement. One hundred twenty-one patients (25.2%) had portal vein thrombosis, mainly in the right portal vein branches (11.7%), and 9.5% cases had an extrahepatic dissemination, mostly to the lymph nodes (4.2%) and lungs (3.3%). Microwave ablation (29%) and TACE (26.4%) were the most common cancer-directed therapies reported in 67.7% patients. (55.4%)

3.2 Association Between ALBI Grade and Child–Pugh Classification

Of the 480 patients enrolled, 154 patients (32%) were classified as ALBI grade 1, 270 patients (56%) as ALBI grade 2, and 56 patients (12%) as ALBI grade 3 (Table 2). Most of the patients with ALBI grade 1 (144 out of 154 patients, 93.5%) had a Child Pugh score of A. Patients were categorised into 4 groups based on their Child Pugh score and ALBI grade (Table 3)

Table 2: Correlation between the ALBI grade and Child Pugh score

ALBI/Child Pugh score	Child Pugh Score – n (%)			
	5	6	≥ 7	Total
ALBI grade				
1	131 (85.1)	13 (8.4)	10 (6.5)	154
2	96 (35.7)	98 (36.4)	76 (28.2)	270
3	0	5 (8.8)	51 (89.5)	56
Total	227	116	137	480

Abbreviations: ALBI-Albumin-Bilirubin

Table 3: Patient Distribution According to Child–Pugh Classification and ALBI Grade

Group	Group details	N
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Group 1	Child Pugh score A5 with ALBI grade 1	131
Group 2	Child Pugh score A5 with ALBI grade 2	96
Group 3	Child Pugh score A6 with ALBI grade 1,2,3	116
Group 4	Child Pugh score ≥ 7 with ALBI grade 1,2,3	137

Abbreviations: ALBI-Albumin-Bilirubin

3.3 Response to lenvatinib

Out of the 480 patients, only 373 (77.7%) were evaluable according to mRECIST criteria, as 107 patients did not undergo repeat imaging as recommended by the HCC management guidelines. Repeat imaging as per mRECIST was advised every six months; however, only a limited number of patients underwent imaging at the recommended interval, with many receiving follow-up scans only when liver function tests became abnormal or when clinical progression was suspected. No patient had a complete response, and only 9 (2.4%) had a partial response to lenvatinib treatment. Stable disease or progressive disease was observed in the majority of patients, 169 (45.3%) and 196 (52.5%), respectively. Tumour response to lenvatinib according to mRECIST is summarised in Table 4.

Table 4: Tumour Response to lenvatinib According to mRECIST Criteria

Group	n	PR	SD	PD	Total evaluable	DCR (%)
Group 1	131	5 (55.6)	51 (30.2)	57 (29.1)	113	49.6
Group 2	96	2 (22.2)	41 (24.3)	42 (21.4)	84	51.2
Group 3	116	0	42 (25)	42 (21.4)	84	50.0
Group 4	137	2 (22.2)	55 (33)	55 (28.1)	92	61.9
Total	480	9	169	196	373	47.7

Abbreviations: ALBI-Albumin-Bilirubin; PR-Partial response; SD- stable disease; PD- progressive disease; DCR: disease control rate

Group 1 (ALBI grade 1) demonstrated comparatively better disease control than the other groups. In particular, the disease control rate (DCR = PR + SD / total number of evaluable patients) for group 1 was 49%, whereas 51.2% for group 2, 50% for group 3, and 61.9% for group 4. Group 1 showed better clinical efficacy among the patients with preserved hepatic function. These findings suggest that, in comparison to patients with higher ALBI grades, group 1 represents patients with preserved liver function and better disease stabilisation during lenvatinib therapy.

3.4 Treatment modifications and discontinuations

The dose modifications and therapy discontinued profiles for each of the four study groups are summarised in Table 5. Forty-two patients had a dose reduction, with group 1 having 36% followed by group 2 (29%) and group 3 (21.4%). Sixty-six individuals experienced drug interruptions, with group 4 experiencing the highest frequency (33.3%). Group 1 showed the highest likelihood of continued treatment (68, 29.2%), whereas treatment discontinuation due to adverse events/progression was more frequent in group 4 (53, 38.1%).

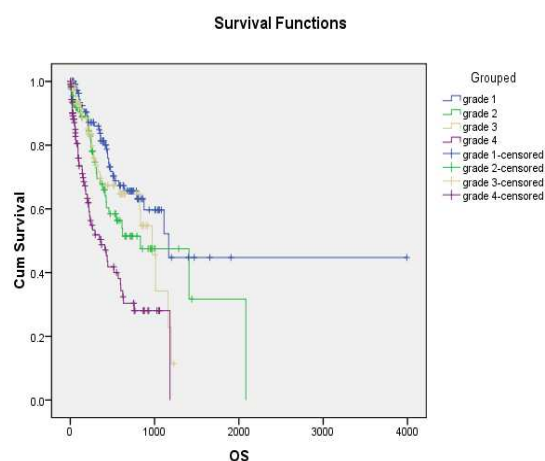
Table 5: Dose Adjustment and Therapy Discontinuation Profile

Group	n	DR	DI	DC due to adverse events	DC due to progression	Ongoing
Group 1	131	15 (36)	17 (26)	7 (25)	24 (22)	68 (29.2)
Group 2	96	12 (29)	14 (21.2)	3 (10.7)	23 (20)	44 (18.9)
Group 3	116	9 (21.4)	13 (19.7)	10 (35.7)	19 (17)	65 (28)
Group 4	137	6 (14.3)	22 (33.3)	8 (28.6)	45 (41)	56 (24)
Total	480	42	66	28	111	233

Abbreviations: DR- Dose reduction; DI- Drug interruptions, DC-Discontinued

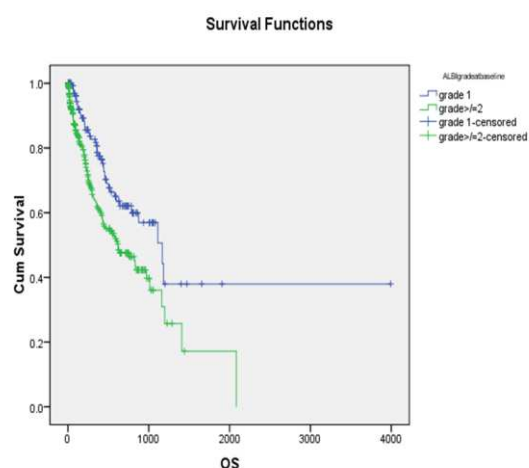
3.5 Survival outcomes (OS, PFS, and TTF) according to ALBI grade and Child Pugh score

The median OS of the present study population was 27.4 months (95% CI 19.2 – 35.5 months). The median OS of patients with groups 1,2,3, and 4 were 38.4, 27.4,32 and 12 months, respectively, with a significant difference among the 4 groups ($p < 0.001$) [Figure 2]. The median OS of patients with ALBI grade 1 and ALBI grade ≥ 2 were 38.4 and 20.4 months, respectively ($p < 0.001$) [Figure 3].



Groups	Median survival (months)	Std. Error	95% CI		P value
			LB	UB	
Group 1	38.4	201.77	25.4	51.4	<0.001*
Group 2	27.4	255.44	10.8	43.8	
Group 3	32	80.73	26.7	37.1	
Group 4	12	89.69	6.2	17.7	

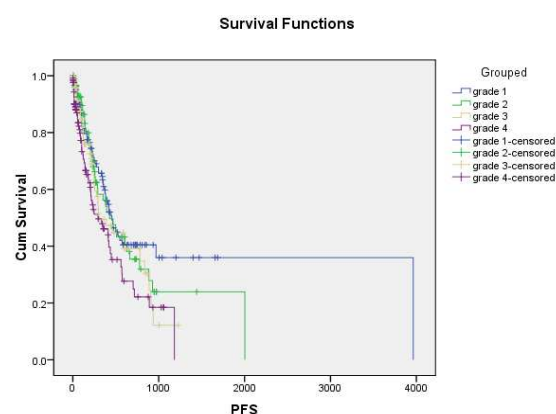
Figure 2. Kaplan Meir curve with a table depicting the overall survival between 4 groups



Groups	Median survival (months)	Std. Error	95% CI		p value
			LB	UB	
Grade 1	38.4	210.65	24.8	51.9	0.001
Grade ≥ 2	20.4	128.15	12.1	28.6	

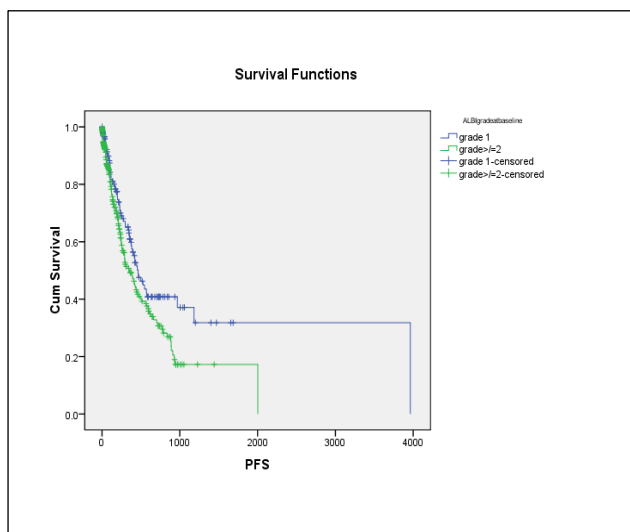
Figure 3. Kaplan Meir curve with a table depicting the overall survival between ALBI grade 1 and ≥ 2

The median PFS of patients with groups 1,2,3, and 4 were 15, 14.1, 10 and 9.7 months, respectively, with a significant difference among the 4 groups ($p = 0.03$) [Figure 4]. The median PFS of patients with ALBI grade 1 and ≥ 2 were 15.3 and 11.5 months, respectively ($p = 0.022$) [Figure 5].



Groups	Median survival (months)	Std. Error	95% CI		P value
			LB	UB	
Group 1	15	52.01	11.57	18.2	0.03*
Group 2	14.1	81.05	8.8	19.3	
Group 3	10	102.07	3.4	16.5	
Group 4	9.7	95.05	11.4	15.6	

Figure 4. Kaplan-Meier curve with a table depicting the progression-free survival between 4 groups

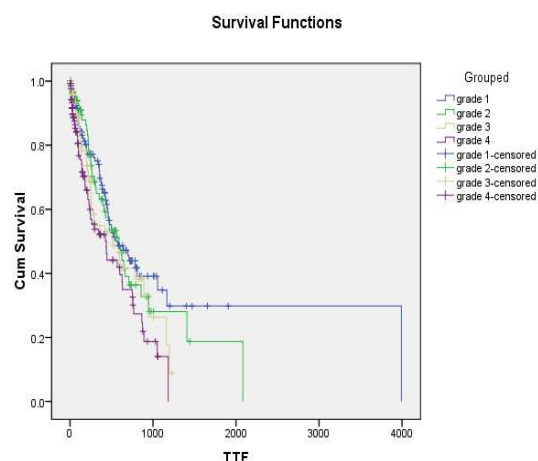


Groups	Median survival (months)	Std. Error	95% CI		p value
			LB	UB	
Grade 1	15.3	57.45	11.5	18.9	0.022
Grade >=2	11.5	46.24	8.5	14.5	

Figure 5. Kaplan Meier curve with a table depicting the progression-free survival between ALBI grade 1 and ≥ 2

The median survival was 17 months (95% CI 14 – 20.1 months). Kaplan Meier estimates of TTF according to ALBI grade and Child Pugh score are shown in Figure

6. The median TTF was 19, 19.4, 17, and 14.4 months in groups 1,2,3, and 4, respectively. Liver function according to the ALBI grade and Child Pugh score was significantly associated with TTF patients of group 2 had the longest TTF, whereas the group 4 patients had the shortest TTF ($p = 0.023$).



Groups	Median survival (months)	Std. Error	95% CI		P value
			LB	UB	
Group 1	19	108.89	12	26	0.023*
Group 2	19.4	94.06	13.3	25.4	
Group 3	17	155.64	7	27	
Group 4	14.4	97.10	8.1	21	

Figure 6. Kaplan Meir curve with a table depicting the time to treatment failure between 4 groups

3.6 Treatment-related adverse events stratified by ALBI grade

The distribution of treatment-related adverse events among patients categorised by ALBI is shown in Table 6. Patients with ALBI grade 2 had a higher overall incidence of any grade adverse events than those with grade 1, but those with ALBI grade 3 had fewer total adverse events, which is probably due to shorter treatment duration and

lower hepatic reserve. The most frequent adverse event in the present study population was fatigue (144, 30%); loss of appetite (106, 22.1%); hand-foot skin reaction (66, 14%); elevated aspartate aminotransferase/ alanine transaminase (49,10.2%); abdominal pain (39, 8.1%), and mucositis (39, 8.1%).

Table 6: Comparison of Treatment-related Adverse Events Among ALBI Grades

Adverse events	ALBI grade 1 (n = 154)		ALBI grade 2 (n = 270)		ALBI grade 3 (n = 56)	
	Any grade	Grade ≥ 2	Any grade	Grade ≥ 2	Any grade	Grade ≥ 2
Fatigue	46	3	84	7	14	0
Loss of appetite	24	1	61	4	16	2
HFSR	21	9	41	20	4	1
Elevated AST/ALT	8	0	27	1	14	1
Abdominal pain	7	0	28	2	4	0
Mucositis	10	0	27	4	2	0
Hypoalbuminemia	9	4	16	6	12	6
Loss of weight	14	1	20	1	1	0
Constipation	9	0	18	0	2	0
Ascites	2	0	16	0	9	1
Diarrhoea	6	1	19	2	2	0
Edema	3	0	17	0	1	0
Dysphonia	8	0	10	1	0	0
Hyperbilirubinemia	3	0	11	1	2	1

Abbreviations: ALBI-Albumin-Bilirubin; HFSR- Hand-Foot Skin Reaction ; AST- Aspartate Aminotransferase; ALT- Alanine Aminotransferase

The most often reported adverse event, mostly of grade 1 severity among ALBI grade 1 patients, was fatigue (29.9%), loss of appetite (15.6%), and HFSR (13.6%). These adverse events were similarly prevalent in ALBI grade 2, whereas grade ≥ 2 events, such as HFSR (7.4%), fatigue (2.6%), and hypoalbuminemia (2.2%), were more prevalent. Overall, patients with ALBI grade 1 showed a decreased likelihood of experiencing severe (grade ≥ 2) adverse events, indicating that hepatic function preservation may improve the treatment tolerance and lessen the risk of toxicity during lenvatinib therapy.

3.7 Univariate and multivariate analysis

Univariate logistic regression was performed to evaluate the association between baseline clinical variables and lenvatinib discontinuation. Factors assessed included age, sex, viral aetiology, AFP levels, BCLC stage, ALBI grade, portal vein thrombosis, number of focal lesions, extrahepatic spread, and initial dose.

In the univariate analysis, the presence of portal vein thrombosis (OR = 1.56; 95% CI: 0.99–2.46; $p = 0.052$), multiple focal lesions (OR = 1.51; 95% CI: 0.97–2.35; $p = 0.064$), and extrahepatic spread (OR = 1.82; 95% CI: 0.93–3.56; $p = 0.078$) showed a trend toward higher odds of discontinuation, though not statistically significant.

Variables with $p < 0.1$ in the univariate analysis were included in the multivariate logistic regression model. In the multivariate analysis, none of the factors retained statistical significance; however, portal vein thrombosis (adjusted OR = 1.47; 95% CI: 0.93–2.33; $p = 0.097$), extrahepatic spread (adjusted OR = 1.75; 95% CI: 0.89–3.46; $p = 0.107$), and multiple focal lesions (adjusted OR = 1.49; 95% CI: 0.95–2.33; $p = 0.079$) remained near-significant predictors of lenvatinib discontinuation (Supplementary material 1).

With regard to factors contributing to disease progression, the results of univariate analysis suggest that both initial dose and extrahepatic spread showed a statistically

significant association with disease progression ($p < 0.001$ for both). Patients receiving higher initial doses (8 or 12 mg) had an increased likelihood of progression (OR = 2.10, 95% CI 1.39–3.16), and those with extrahepatic spread demonstrated a markedly higher risk (OR = 3.69, 95% CI 1.79–7.63). The multivariate analysis confirmed initial dose (OR = 1.95, 95% CI 1.29–2.97, $p = 0.002$) and extrahepatic spread (OR = 3.59, 95% CI 1.69–7.60, $p = 0.001$) as independent predictors of disease progression. Although BCLC stage C showed a trend toward higher risk (OR = 1.66, 95% CI 0.97–2.85, $p = 0.064$), it did not reach statistical significance (Supplementary material 2).

Patients who received cancer-directed therapy demonstrated significantly longer survival outcomes compared to those who did not. The mean OS was 46 months in patients who underwent cancer-directed therapy versus 17.6 months in those without ($p < 0.001$). Similarly, the mean PFS was significantly higher among patients receiving cancer-directed therapy (33.7 months vs. 12.9 months; $p = 0.003$). Among individual treatment modalities, TACE showed a significant improvement in both OS (62.1 months vs. 28.8 months; $p < 0.001$) and PFS (43 months vs. 22.5 months; $p = 0.029$). Liver transplantation also demonstrated a significant benefit in PFS ($p = 0.047$). Other modalities such as RFA, MWA, TARE, and SBRT did not show statistically significant differences in survival outcomes (Supplementary material 3).

Discussion

Our study is one of the largest real-world assessments from South India evaluating the prognostic role of ALBI score in patients receiving lenvatinib treatment for advanced HCC. These findings demonstrate a correlation between the treatment outcomes and survival in this cohort. The treatment paradigm for advanced HCC has changed as a result of recent advancements in systemic therapy. In patients with Child Pugh A liver function and an ECOG performance status of 0-1, the ASCO 2024 guidelines suggest immune checkpoint inhibitor combinations, such as atezolizumab plus bevacizumab or durvalumab plus tremelimumab, as the preferred first-line treatment^{7,12}. However, lenvatinib continues to play a crucial role in clinical practice when immunotherapy is contraindicated or unavailable⁸.

The study cohort's demographic profile is consistent with regional and global HCC epidemiology, which consistently shows a predominance of older age and males²²⁻²⁴. The epidemiological landscape of HCC in India is evolving with alcohol related liver disease and metabolic dysfunction-associated steatosis (MASLD) exceeding the viral causes in recent years^{25,26}. These changes emphasize the importance of regional real-world data to comprehend treatment outcomes in a variety of hepatic backgrounds. Given that other studies have demonstrated equivalent efficacy but superior safety profiles at lower doses in patients with impaired hepatic reserve, the larger percentage of patients receiving a lower dose of lenvatinib (4mg OD) may reflect the dosage individualization based on hepatic function and tolerability^{11,27}.

The overall objective response rate (ORR) was low (2.4%), and the disease control rate (DCR) was 47.7% in this real-world cohort. When compared to the pivotal REFLECT study, which revealed an ORR of 24.1% and DCR of 75.5% according to mRECIST criteria, these results are modest¹¹. The inclusion of individuals with impaired hepatic function (ALBI grade 2 and 3), varying drug exposure, could be the reason for the reduced efficacy seen in our study. Group 1 (ALBI grade 1) demonstrated a comparatively positive response profile with a lower rate of PD and a greater PR proportion. This suggests that disease stabilisation with ALBI grade 1 patients is more durable and linked to better survival outcomes. Prior research has shown that patients with baseline liver function (ALBI grade 1 or Child Pugh A) achieve significantly improved ORR, DCR, PFS, and OS²⁸⁻³⁰.

According to Hiraoka et al, DCR for ALBI grades 1 and 2 were 3% and 55% respectively, along with a median PFS of 8.9 and 4.2 months²⁸. Early detection of biochemical and radiological responses is considered a prognostic marker of better survival in patients with preserved hepatic function, as reported by Kodama K et al²⁴. A study by Shimozato et al³¹ and Cheon et al³² from Japanese and Korean cohorts, respectively, reported that lenvatinib yielded better outcomes among patients with ALBI grade 1. The above studies support the need for preserved liver function can enhance lenvatinib's anti-cancer activity and disease control potential.

The key factors for tolerability and safety in lenvatinib-treated HCC patients are treatment modifications and discontinuation. Group 1 showed a lower frequency of

dose interruptions and adverse event-related discontinuations compared to other groups. A higher rate of ongoing therapy (29.2%) was also observed in this group. Consistent with our findings, prior real-world studies have demonstrated that 10-25% of patients on lenvatinib discontinue treatment due to adverse events. According to Kudo et al, 18% of the participants of the REFLECT study¹¹ discontinued due to adverse events, demonstrating controllable toxicity with suitable dose modification techniques. Ikeda et al also showed that dose reductions and interruptions did not substantially affect treatment efficacy, highlighting the significance of personalised dosing to preserve tolerability³³. The higher discontinuation rates in group 4 of our cohort could be attributed to advanced disease stage or impaired hepatic function^{34,35}. These results emphasize that, especially in individuals with good hepatic reserve, dose individualization and close monitoring of adverse events can help maintain therapy with enhanced outcomes.

Our results are in line with other international studies by Tada et al and Hiraoka et al, which showed that the patients with ALBI grade 1 had considerably longer PFS and OS than patients with higher ALBI grades^{18,14}. The median OS for ALBI grade 1 patients in our dataset was 38.4 months, while the median OS for ALBI grade ≥ 2 was 20.4 months, which closely matches the real-world assessments conducted in Italy and Japan^{13,36}. Hepatic reserve is crucial for maintaining lenvatinib therapy as it is linked to fewer treatment discontinuations and dose interruptions. Compared to patients treated with lenvatinib alone, those who received prior or concurrent cancer-directed therapy, such as TACE, MWA, resection, or liver transplantation, have noticeably better survival rates. These findings support the concept of multimodal management with both locoregional and systemic treatment to promote tumour control^{7,37}. Specifically, our study's median OS exceeded 60 months when TACE and lenvatinib were combined, which is consistent with emerging data from East Asian cohorts that sequential or combinational treatment can improve outcomes in well-compensated patients³⁸.

Fatigue, anorexia, and HFSR were the most common toxicities in our study's adverse event profile, which was similar to earlier real-world findings³⁹. As hepatic function declined (ALBI grade ≥ 2), their occurrence increased, highlighting the significance of liver function-based dose selection. These insights align with the earlier empirical

findings. Compared to ALBI grade 1, Hiraoki et al²⁸ found that ALBI grade 2 patients had a greater risk of therapy termination and dose reductions due to hepatotoxicity. Similarly, in HCC patients receiving lenvatinib, Ueshima et al³⁸ found that baseline ALBI grade was an independent predictor of both survival and hepatic adverse events. Increased toxicity and decreased dosage intensity were also observed in patients with poorer baseline liver function in an Indian multi-centric experience by Rauthan A et al,⁴⁰ confirming the use of ALBI grade as a useful tool for treatment planning.

In line with the findings of Burgio V et al³⁶, multivariate analysis showed that extra-hepatic spread and higher initial dose independently predict the progression of disease. Since the patients with advanced tumour burden or BCLC stage C usually receive higher initial doses, the correlation between the higher dosage and advanced disease may be due to aggressive disease biology. All of these findings substantiate the current study's findings that lenvatinib's anti-cancer efficacy and disease control rate are enhanced by preserved liver function (ALBI grade 1). For HCC patients on lenvatinib therapy, baseline ALBI assessment should be regarded as a crucial stratification tool for maximizing treatment results, identifying the best dose, forecasting tolerance, and guiding clinical decision-making on patients receiving sequential or combinational therapy.

There are certain limitations of our study. Due to the single-centre retrospective nature of the analysis, selection bias and missing imaging data are present. Furthermore, the measurement of temporal changes in hepatic reserve was not possible due to the lack of a dynamic assessment of ALBI during therapy. Despite these drawbacks, our results are strengthened by the large cohort size and uniform treatment protocol. Notably, our study offers region-specific data from an Indian population where HCC aetiology, comorbidities, and clinical presentation differ from Western and East Asian cohorts, thereby helping to bridge a key evidence gap.

Conclusion:

In conclusion, lenvatinib improved tumour response and disease control in patients with ALBI grade 1, which may result in increased treatment efficacy and longer survival. The prognostic and predictive utility of ALBI grading in clinical practice is supported by these results.

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Conflicts of Interest:

All the authors declare no competing interests.

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Data Availability:

All data generated or analysed during this study are included in this published article [and its supplementary information files]

Ethical approval and informed consent to participate:

This study was approved by the Institutional Ethics Committee of Amrita School of Medicine ECASM-AIMS-2021-293 on 15-06-2021. It was conducted as per the principles of the Declaration of Helsinki and guidelines of the Indian Council of Medical Research. All authors certify that they have obtained all appropriate individual patient informed consent (oral/written) after a clear discussion with the patient/bystander for the study. The study participants were made aware of the study purpose, risks, and benefits.

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References:

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin*. 2024;74(1):12-49.
2. Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. Lyon: IARC; 2024 [Internet]. Available from: <https://gco.iarc.who.int/today>. Accessed 22 Oct 2025.
3. Giri S, Singh A. Epidemiology of hepatocellular carcinoma in India—an updated review for 2024. *J Clin Exp Hepatol*. 2024;14(6):101447.
4. International Agency for Research on Cancer. GLOBOCAN 2022 India fact sheet. Lyon: IARC; 2022 [Internet]. Available from: <https://gco.iarc.who.int/media/globocan/factsheets/populations/356-india-fact-sheet.pdf>. Accessed 27 Oct 2025.
5. Musunuri B, Shetty S, Bhat G, Udupa K, Pai A. Profile of patients with hepatocellular carcinoma: An experience from a tertiary care centre in India. *Indian J Gastroenterol*. 2022;41(2):127–134.
6. Koshy A, Devadas K, Panackel C, Philip M, Premaletha N, Zacharias P et al.; Kerala Hepatocellular Carcinoma Study Group. Multi-center prospective survey of hepatocellular carcinoma in Kerala: More than 1,200 cases. *Indian J Gastroenterol*. 2023;42(2):233–240.
7. Kumar K, Saraswat VA. Evolving landscape of systemic therapy for hepatocellular carcinoma in 2025. *J Clin Exp Hepatol*. 2025;102547. doi:10.1016/j.jceh.2025.102547.
8. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382(20):1894-1905.

9. Kudo M. Lenvatinib versus sorafenib in first-line treatment of unresectable hepatocellular carcinoma: REFLECT trial and beyond. *Liver Cancer*. 2017;6(1):1-9. doi:10.1159/000452868.
10. Chen Y, Dai S, Cheng C, Cheng L. Lenvatinib and immune checkpoint inhibitors in hepatocellular carcinoma: mechanistic insights, clinical efficacy and future perspectives. *J Hematol Oncol*. 2024;17(1):130.
11. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F et al. Lenvatinib versus sorafenib in first-line treatment of unresectable HCC (REFLECT). *Lancet*. 2018;391(10126):1163-1173.
12. Gordan JD, Kennedy EB, Abou-Alfa GK, Beal E, Finn RS, Gade TP et al. Systemic therapy for advanced hepatocellular carcinoma: ASCO guideline update. *J Clin Oncol*. 2024;42(15):1830-1850.
13. Persano M, Rimini M, Tada T, Suda G, Shimose S, Kudo M, Cheon J et al. Clinical outcomes with atezolizumab plus bevacizumab or lenvatinib in hepatocellular carcinoma: real-world study. *J Cancer Res Clin Oncol*. 2023;149(9):5591-5602.
14. Kang W, Kim YJ, Kim SU, Seo YS, Kim JW, Kim JH et al. Real-world effectiveness and safety of lenvatinib in unresectable hepatocellular carcinoma in Korea: post marketing study. *Future Oncol*. 2024;20(37):2949-2959.
15. Casadei-Gardini A, Rimini M, Kudo M, Shimose S, Tada T, Suda G et al. Real life Study of Lenvatinib therapy for hepatocellular carcinoma: RELEVANT study. *Liver Cancer*. 2022;11(6):527-539.
16. Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach- the ALBI grade. *J Clin Oncol*. 2015;33(6):550-558.
17. Toyoda H, Johnson PJ. The ALBI score: From liver function in patients with HCC to a general measure of liver function. *JHEP Rep*. 2022;4(10):10057.
18. Tada T, Kumada T, Hiraoka A, Atsukawa M, Hirooka M, Tsuji K, Ishikawa T et al. Impact of modified albumin-bilirubin grade on survival in patients with HCC who received lenvatinib. *Sci Rep*. 2021;11: 14474.
19. Shafiq S, Khan MN, Majumder B, Alam MS, Islam MS, Sultana T. Correlation of Albumin-Bilirubin (ALBI) score with Child-Turcotte-Pugh (CTP) score in the evaluation of liver cirrhosis. *Am J Lab Med*. 2019;4(3):60–64.

20. Sinha N, Porwal J, Sehrawat A, Mitra R, Gargy S. Comparison of Child–Turcotte–Pugh score and albumin–bilirubin index score for advanced hepatocellular carcinoma at an LMIC tertiary cancer facility. *J Clin Oncol*. 2023;41(16 Suppl):e16174.
21. Peng Y, Wei Q, He Y, Xie Q, Liang Y, Zhang L, et al. ALBI versus Child-Pugh in predicting outcome of patients with HCC: A systematic review. *Expert Rev Gastroenterol Hepatol*. 2020;14(5):383–400.
22. Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. *Nat Rev Gastroenterol Hepatol*. 2019;16(10):589-604.
23. Villanueva A. Hepatocellular carcinoma. *N Engl J Med*. 2019;380(15):1450-1462.
24. Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S et al. Hepatocellular carcinoma. *Nat Rev Dis Primers*. 2021;7(1):6.
25. Eslam M, Sanyal AJ, George J, & International Consensus Panel. MAFLD: A consensus-driven proposed nomenclature for Metabolic Associated Fatty Liver Disease. *Gastroenterology*. 2020;158(7):1999-2014.e1.
26. Duseja A, Chalasani N. Epidemiology and risk factors of NAFLD. *Hepatol Int*. 2013;7(S2):755-764.
27. Pires Amaro C, Allen MJ, Knox JJ, Tsang ES, Lim HJ, Richard M et al. Dosing, efficacy and safety of lenvatinib—Canadian real-world data. *Liver Cancer Int*. 2022; 3:119-127.
28. Hiraoka A, Kumada T, Kariyama K, Takaguchi K, Atsukawa M, Itobayashi E et al. Clinical features of lenvatinib for unresectable HCC: multicenter analysis. *Cancer Med*. 2019;8(1):137-146.
29. Kodama K, Kawaoka T, Namba M, Uchikawa S, Ohya K, Morio K et al. Correlation between early tumor marker response and imaging response in patients with advanced hepatocellular carcinoma treated with lenvatinib. *Oncology*. 2019;97(2):75-81.
30. Kuzuya T, Ishigami M, Ito T, Ishizu Y, Honda T, Ishikawa T et al. Favorable radiological antitumor response at 2 weeks after starting lenvatinib for patients with advanced hepatocellular carcinoma. *Hepatol Res*. 2020;50(3):374-381.
31. Shimozato N, Namisaki T, Okano A, Ohana M, Kinoshita D, Kawasaki T et al. Efficacy and safety of lenvatinib for patients with advanced hepatocellular

- carcinoma: A retrospective, real world study conducted in Japan. *Anticancer Res.* 2022;42(1):173-183.
32. Cheon J, Chon HJ, Bang Y, Park NH, Shin JW, Kim KM, et al. Real-world efficacy and safety of lenvatinib in Korean patients with advanced hepatocellular carcinoma: a multicenter retrospective analysis. *Liver Cancer.* 2020;9(5):613–24.
 33. Ikeda M, Okusaka T, Mitsunaga S, Ueno H, Tamai T, Suzuki T et al. Safety and pharmacokinetics of lenvatinib in advanced HCC. *Clin Cancer Res.* 2016;22(6):1385-1394.
 34. Hiraoka A, Kumada T, Atsukawa M, Hirooka M, Tsuji K, Ishikawa T et al. Early relative change in hepatic function with lenvatinib. *Oncology.* 2019;97(6):334-340.
 35. Reig M, Forner A, Rimola J, Ferrer-Fabrega J, Burrel M, Garcia-Criado A et al. BCLC strategy for HCC: 2022 update. *J Hepatol.* 2022;76(3):681-693.
 36. Burgio V, Iavarone M, Di Costanzo GG, Marra F, Lonardi S, Tamburini E et al. Real life data of Lenvatinib vs sorafenib for unresectable HCC in Italy. *Cancer Manag Res.* 2021;13:9379-9389.
 37. Peng Z, Fan W, Zhu B, Wang G, Sun J, Xiao C et al. Lenvatinib plus Transarterial Chemoembolization as first-line treatment for Advanced Hepatocellular carcinoma: A Phase III, Randomized Clinical Trial (LAUNCH). *J Clin Oncol.* 2023;41(1):117-127.
 38. Ueshima K, Nishida N, Hagiwara S, Aoki T, Minami T, Chishina H et al. Impact of baseline ALBI grade on the outcomes of hepatocellular carcinoma patients treated with lenvatinib. *Cancers (Basel).* 2019;11(7):952.
 39. Sho T, Suda G, Ogawa K, Kimura M, Shimazaki T, Maehara O et al. Early response and safety of lenvatinib for patients with advanced hepatocellular carcinoma in a real world setting. *JGH Open.* 2019; 4 (1):54-60.
 40. Rauthan A, Somashekhar SP, Patil P, Zaveri S. Real-world experience with lenvatinib in HCC—Indian single-center experience. *J Clin Oncol.* 2020;38(15_suppl):e16596.

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