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The Role of Liver Stiffness Measurement in Advanced Hepatocellular Carcinoma

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Abstract

Introduction: Liver stiffness measurement (LSM) by transient elastography is associated with risks of HCC and post-surgical outcomes of patients undergoing hepatectomy. However, the role of LSM in patients with advanced HCC is less clear. **Methods:** Patients with a confirmed diagnosis of HCC were prospectively recruited from March 2013 to April 2019. Prior to commencing treatment for HCC, all patients underwent transient elastography (FibroScan®) by hepatologists. The LSM reading, baseline characteristics, and tumor information of patients were recorded. All patients were followed up prospectively for survival events. **Results:** A total of 165 patients with HCC were recruited. The median follow-up was 40.6 months. The median overall survival was 11.9 months. The median age was 62 years with 77% having chronic hepatitis B. Most patients (69.7%) underwent non-surgical treatment (including transarterial chemoembolization and systemic therapy) and supportive care (19.4%) whereas the remaining patients (10.9%) underwent surgery. The median LSM was 26.3kPa (Range = 3.5–75), where the closest integral of 30kPa was chosen as a cut-off for analyses. LSM was correlated with the diameter of the right lobe tumor (R = 0.463; $p < 0.0001$). It was also correlated with a more advanced BCLC stage ($p = 0.0006$) and worse ALBI grade ($p = 0.0002$). Patients with LSM > 30kPa had worse OS than patients with LSM ≤ 30kPa (Median OS = 5.4 months, 95% CI [2.7-8.1] [> 30kPa] vs 21.2 months, 95% CI [17.6–24.7] [≤ 30kPa]; HR = 2.156; [95% Cl = 1.514-3.069]; $p = 0.0001$). In multivariable analysis, LSM > 30kPa remained an independent predictor of survival after adjustment with ALBI grade, ALP, and BCLC stage. **Discussions:** An LSM > 30kPa is a significant and independent predictor of survival for HCC.

Keywords

Chronic hepatitis B; transient elastography; FibroScan; liver fibrosis

1. Introduction

Liver fibrosis is the excessive accumulation of extracellular proteins including collagen that occurs in most types of chronic liver diseases [1]. It is associated with hepatic function in patients with chronic liver diseases or HCC. Transient elastography is a non-invasive method for the assessment of liver fibrosis [2]. It measures liver stiffness, a surrogate marker of liver fibrosis, by the placement of a probe emitting a shear wave through the liver and the measurement of the velocity of

the wave in the liver. The tool has been validated in measuring hepatic fibrosis across different patient groups with chronic liver disease [3–5]. In chronic hepatitis B patients with normal alanine transaminase (ALT) levels, a liver stiffness of > 9 to 12kPa is diagnostic of bridging fibrosis while liver stiffness of > 12kPa is associated with a specificity of 95% in the diagnosis of liver cirrhosis [3].

In recent years, liver stiffness measurement (LSM) has been shown to predict the risks of the development of hepatocellular carcinoma (HCC), as well as provide information on treatment outcomes for patients with HCC. Higher LSM is associated with increased risks of HCC development [6]. The role of LSM in predicting surgical risks for HCC patients has also been studied. One paper suggests that there is a direct correlation between LSM and the occurrence of portal hypertension in HCC populations, and it can be used to evaluate the surgical risks in HCC patients with Child-Pugh A status [7]. Another paper suggests that LSM can predict postoperative liver failure in patients undergoing hepatectomy for HCC [8].

The role of LSM in patients with more advanced HCC who are unsuitable for surgical treatment is less clear. Theoretically, higher LSM signifies worse liver fibrosis and hepatic reserves which impact the treatment outcomes of non-surgical treatment [9,10]. However, there is a lack of studies to evaluate the role of LSM in patients undergoing non-surgical treatment. This is partly because the presence of a tumor in the right lobe of the liver may influence the LSM reading. In the current study, we aim to evaluate the prognostic role of LSM in a cohort of patients with HCC of different stages.

2. Methods

2.1. Patients

A prospective cohort of patients with a first-time confirmed diagnosis of HCC treated at the Prince of Wales Hospital, Hong Kong, was consecutively enrolled from Mar 2013 to Apr 2019. Key inclusion criteria included patients with a confirmed diagnosis of HCC according to the American Association for the Study of Liver Diseases criteria [11] who are willing to undergo study procedures. Key exclusion criteria included patients with Eastern Cooperative Oncology Group (ECOG) performance status of 3 or higher; the presence of poorly controlled ascites; and expected life expectancy of 8 weeks or shorter. The study was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Research Ethics Committee.

2.2. Evaluation

After obtaining consent, baseline characteristics, laboratory parameters, and tumor-related features were documented for each patient within 1 week from the transient elastography (FibroScan®). Transient elastography was arranged within 4 weeks of commencing the first-line treatment for HCC and conducted by experienced hepatologists at the Department of Medicine and Therapeutics of the hospital as per the manufacturer's instruction. Ten successful readings were obtained on each patient in the right lobe of the liver. The median value of LSM was documented and the results were expressed in kilopascals (kPa). All patients were followed up by the clinical investigators at the Department of Clinical Oncology at the Prince of Wales Hospital till death, loss of follow-up, or withdrawal of consent from the study.

2.3. Statistical Analysis

Patient characteristics were summarized by descriptive statistics. Continuous variables were expressed as mean with standard deviation or median with range, as appropriate. Categorical variables were presented as counts (percentage). For the analysis of proportional endpoints (from the date of recruitment to death or the end of the study in June 2021), estimated proportions together with 95% confidence intervals (CIs) were calculated. Comparisons between proportions were made using homogeneity Chi-square tests. The correlation between LSM and tumor diameter in the right lobe of the liver was examined by Spearman's test. Overall survival (OS) and median survival were estimated by the Kaplan-Meier method with 95% CIs. To examine the independent effect on the prognostication of the liver stiffness and other relevant parameters, multivariate analysis by the Cox proportional hazards model was performed using a stepwise model-building procedure based on a significance value of $p < 0.05$ for both inclusion and exclusion into the system. The statistical analysis was performed by using the statistical software SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patients

A total of 165 patients were consecutively recruited from March 2013 to April 2019. The baseline characteristics of the patients including the demographics, organ function as well as tumor stages and characteristics are summarized in **Table 1**. In summary, the median age was 62 years with 77% having chronic hepatitis B infection. One hundred and thirty-five patients had a disease load in the right lobe of the liver with a median diameter of 8.9 cm. Most patients (69.7%) underwent non-surgical treatments, including transarterial chemoembolization (TACE) and systemic therapy. Eighteen (10.9%) underwent surgery and 32 (19.4%) patients received the best supportive care as the primary treatment. One hundred and twenty-seven patients died and thirty-eight patients were alive at the time of data cut-off for analysis in June 2021. The median follow-up duration of patients was 40.6 months, and the median OS was 11.9 months (95% CI: 8.1–15.6 months).

3.2. Liver Stiffness Measurement

The results of LSM are summarized in **Table 2**. The median LSM of the whole study population was 26.3kPa (Range: 3.5–75kPa). The closest integral of 30kPa was chosen as the cut-off for LSM correlation and survival analyses. Seventy-five people (45.5%) had LSM > 30kPa. The LSM value for patients undergoing surgery, TACE, systemic therapy, and supportive care was 16.6 kPa, 10.4 kPa, 38.0 kPa, and 49.5 kPa, respectively. The proportion of patients with LSM > 30kPa was 61.6% and 65.6% in the systemic therapy and supportive care group respectively, while the corresponding proportion was 29.1% and 5.6% in the TACE group and surgery group.

Table 1: Baseline Characteristics.

	Whole population	Surgery	Non-surgical	Supportive care
Number of patients	165 (100)	18 (10.9)	115 (69.7)	32 (19.4)
Patients' features				
Age (years)				
Mean (SD)	61.2 (11.1)	59.9 (10.2)	61.5 (11.4)	61.2 (10.9)
Median (Range)	62 (27–84)	63 (33–78)	62 (27–84)	63 (40–80)
Sex (Male: Female)	131: 34	14: 4	91: 24	26: 6
ECOG performance status				
0	117 (70.9)	15 (83.3)	81 (70.4)	21 (65.6)
1	48 (29.1)	3 (16.7)	34 (29.6)	11 (34.4)
History of alcohol	81 (49.1)	7 (38.9)	58 (50.4)	16 (50)
HBsAg positive	127 (77.0)	13 (72.2)	87 (75.7)	27 (84.4)
Anti-HCV positive	14 (8.5)	2 (11.1)	11 (9.6)	1 (3.1)
Symptomatic at presentation	59 (35.7)	12 (66.7)	39 (33.9)	8 (25.0)
Vascular invasion	53 (32.1)	1 (5.6)	36 (31.3)	16 (50)
First-line treatment				
Surgery	18 (10.9)	18	0	0
Systemic therapy	60 (36.4)	0	60	0
TACE	55 (33.3)	0	55	0
Supportive care	32 (19.4)	0	0	32
Laboratory parameters				
Bilirubin (μmol/l) (Median; Range)	15; 3–90	12; 6–22	15; 3–90	19.5; 5–78
Albumin (g/l) (Median; Range)	38; 19–47	41; 33–47	38; 19–47	35.5; 25–46
ALT (IU/l) (Median; Range)	45; 10–291	37; 16–110	46; 10–291	42.5; 14–256
ALP (IU/l) (Median; Range)	139; 2–1536	90.5; 47–199	137; 2–712	162; 8–1536
AFP (ng/ml) (Median; Range)	213; 1–1316800	10; 2–5734	124; 1–1316800	2269; 4–990800
Creatinine (μmol/l) (Median; Range)	76; 8.3–179	78; 51–111	76; 8.3–179	77.5; 51–139
Hepatic function				
ALBI				
Grade 1	63 (38.2)	11 (61.1)	45 (39.1)	7 (21.9)
Grade 2	92 (55.8)	7 (38.9)	64 (55.7)	21 (65.6)
Grade 3	10 (6.1)	0 (0)	6 (5.2)	4 (12.5)
Child-Pugh class				
A	131 (80.0)	18 (100)	93 (80.9)	21 (65.6)
B	31 (18.8)	0	22 (19.1)	9 (28.1)
C	2 (1.2)	0	0 (0)	2 (6.3)
Tumorous features				
BCLC stage				
A	21 (12.7)	10 (55.6)	9 (7.8)	2 (6.3)
B	42 (25.5)	3 (16.7)	31 (27.0)	8 (25.0)
C	100 (60.6)	5 (27.8)	75 (65.2)	20 (62.5)
D	2 (1.2)	0 (0)	0 (0)	2 (6.3)
Longest tumor diameter in the liver (cm)				
Mean; SD	8.69; 5.43	4.39; 3.05	8.9; 5.50	10.36; 5.13
Median; Range	8.00; 0.9–25.7	3.10; 1.2–11.1	8.00; 0.9–25.7	9.85; 2.9–20.5
Longest tumor diameter in the right lobe (cm) (N = 135)				

Mean (SD)	8.92; 5.68	4.18; 3.27	9.32; 5.68	9.45; 5.71
Median (Range)	8.00; 0.9–25.7	2.80; 1.4–11.1	8.50; 0.9–25.7	8.95; 1.0–20.5
Tumor number				
Unifocal	66 (40.0)	13 (72.2)	42 (36.5)	11 (34.4)
Multifocal	99 (60.0)	5 (27.8)	73 (63.5)	21 (65.6)

(Abbreviations: AFP, alpha-fetoprotein; ALBI, Albumin-Bilirubin; ALP, alkaline phosphatase; ALT, alanine transaminase; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation; TACE, transarterial chemo-embolization).

Table 2: Liver stiffness measurement.

Whole population (N = 165)	Mean (SD)	Median (Range)
E Med (kPa)	36.5 (26.5)	26.3 (3.5–75)
E IQR (kPa)	5.2 (7.6)	2.2 (0–64.1)
Patients with E Med > 30kPa (%)	75 (45.5)	
TACE (N = 55)	Mean (SD)	Median (Range)
E Med (kPa)	28.9 (24.0)	16.5 (5.8–75)
E IQR (kPa)	5.0 (5.4)	2.2 (0–21.7)
E Med > 30kPa	16 (29.1)	
Systemic therapy (N = 60)	Mean (SD)	Median (Range)
E Med (kPa)	44.5 (26.2)	38.0 (6.8–75)
E IQR (kPa)	5.9 (9.8)	3.1 (0–64.1)
Patients with E Med > 30kPa (%)	37 (61.7)	
Surgery (N = 18)	Mean (SD)	Median (Range)
E Med (kPa)	14.0 (16.1)	10.4 (3.5–75.0)
E IQR (kPa)	1.6 (1.7)	1.4 (0.0–7.8)
Patients with E Med > 30kPa (%)	1 (5.6)	
Supportive care (N = 32)	Mean (SD)	Median (Range)
E Med (kPa)	47.2 (24.8)	49.5 (7.8–75)
E IQR (kPa)	6.1 (7.7)	2.3 (0–28.1)
Patients with E Med > 30kPa (%)	21 (65.6)	

(Abbreviations: E IQR; E Med; SD, standard deviation; TACE, transarterial chemoembolization).

3.3. Clinical Parameters Associated with LSM

In the whole population, higher LSM reading of the patients was correlated with the longer diameter of the tumor in the right lobe (R = 0.464; $p < 0.0001$). Higher LSM reading was also associated with more advanced Barcelona Clinic Liver Cancer (BCLC) stage (i.e., stage C and D) ($p = 0.0006$) and worse Albumin-Bilirubin (ALBI) grade (i.e., grade 2 and 3) ($p = 0.0002$). The above findings were similarly observed in the subgroup of patients undergoing non-surgical treatments (i.e., TACE and systemic therapy). Above findings were summarized in **Table 3**.

3.4. Prognostic Impact of LSM

The median OS of patients with LSM > 30kPa was 5.4 months (95% CI: 2.7–8.1 months), which was shorter than the median OS of patients with LSM ≤ 30kPa (21.2 months, 95% CI: 17.6–24.7 months) (Hazard Ratio [HR] = 2.156 [95% Cl = 1.514–3.069]; $p = 0.0001$) **(Figure 1)**. Amongst patients undergoing non-surgical treatments (i.e. TACE and systemic therapy), similar findings were observed: the median OS of patients with LSM > 30kPa was 7.4 months, 95% CI: 4.3–10.6 months which was shorter than an OS of 19.8 months, 95% CI: 14.0–25.5 months in patients with LSM ≤ 30kPa (HR = 1.757 [95% CI = 1.166–2.649]; $p = 0.007$) **(Figure 2)**. Univariate analyses showed that higher ECOG performance status, the presence of ascites or vascular invasion, symptomatic at presentation, higher serum alpha-fetoprotein, worse Albumin-Bilirubin (ALBI) grade, higher Child-Pugh score were prognostic factors for OS respectively **(Table 4)**. In multivariable analysis **(Table 5)**, LSM > 30kPa remains an independent predictor of survival after adjustment with ALBI grade and alkaline phosphatase (ALP) (AIC = 1098.232) (Model 1) as well as BCLC stage and ALP, (AIC = 1093.120) (Model 2).

4. Discussions

Multiple studies and meta-analyses suggest that LSM measured by transient elastography provided prognostic value on HCC patients undergoing surgery or loco-ablation **[8,12,13]**. For example, a study by our group reports that LSM > 12kPa was an independent prognostic factor for both post-hepatectomy liver failure and major postoperative complications **[14]**.

Another study corroborates that higher LSM was associated with more severe postoperative complications and hence it was a useful preoperative investigation for risk stratification before hepatectomy **[15]**. In patients with more advanced HCC, the prognostic role of LSM is less clear. In the current study, the study population is characterized by a high disease burden with approximately 90% of patients undergoing non-surgical treatments or supportive care and 77% having chronic hepatitis B. In this group of patients, we demonstrated that higher LSM is independently associated with worse survival outcomes. In particular, the survival difference between the two groups, namely with LSM > 30kPa and LSM ≤ 30kPa, is remarkable with an HR of higher than 2. The above findings are potentially clinically important. Unlike surgical candidates, histology is not available in most patients with advanced HCC. Hence histological assessment of liver fibrosis in HCC is not feasible. In this scenario, transient elastography could provide a non-invasive way to assess liver fibrosis **[16]**.

In clinical practice, a number of staging systems are used by clinicians to assess the prognosis of HCC. All those staging systems focus on tumor burden, hepatic reserves, and performance of patients while liver fibrosis is not considered. In the current study, it was found that the prognostication of LSM is independent of BCLC staging and ALBI grade, which suggests that LSM could provide additional information on top of tumor staging or hepatic function. In particular, patients with LSM > 30kPa have a median OS shorter than 6 months. This is of potential clinical relevance to help investigators or clinicians stratify prognoses of patients in clinical trials or clinical practice.

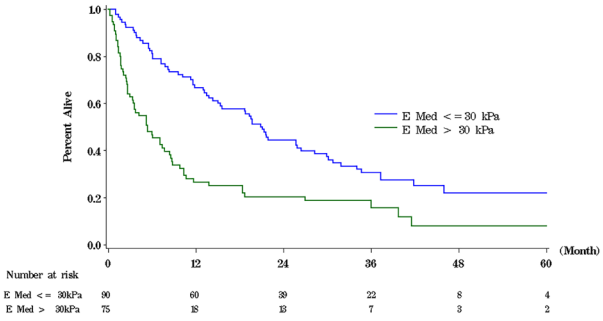

Figure 1: Survival curve of the whole patient population. The median OS of patients with LSM > 30kPa was 5.4 months, which was significantly shorter than the median OS of patients with LSM ≤ 30kPa, at 21.2 months (HR = 2.156; p = 0.0001).

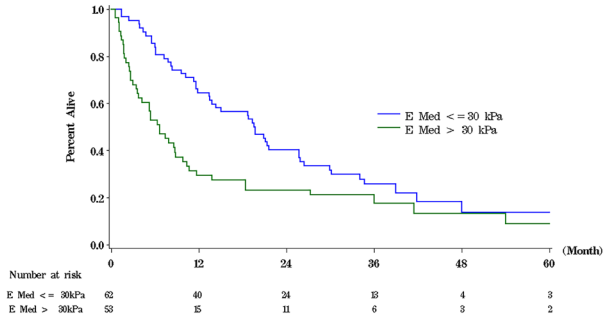

Figure 2: Survival curve of patients undergoing non-surgical treatments. The median OS of patients with LSM > 30kPa was 7.4 months, which was significantly shorter than the median OS of patients with LSM ≤ 30kPa, at 19.8 months (HR = 1.757; p = 0.007).

Table 3: Correlation between LSM and clinical parameters.

LSM and BCLC stage					
Population	N	LSM (E Med)	A-B	C-D	p-value
Whole population (N = 165)	90	≤ 30 kPa	45 (71.4)	45 (44.1)	0.0006
	75	> 30 kPa	18 (28.6)	57 (55.9)	
Non-surgical treatment (N = 115)	62	≤ 30 kPa	28 (70.0)	34 (45.3)	0.0115
	53	> 30 kPa	12 (30.0)	41 (54.7)	
Supportive care (N = 32)	11	≤ 30 kPa	5 (50.0)	6 (27.3)	0.2096
	21	> 30 kPa	5 (50.0)	16 (72.7)	
LSM and ALBI grade					
Population	N	LSM (E Med)	Grade 1	Grade 2-3	p-value
Whole population (N = 165)	90	≤ 30 kPa	46 (73.0)	44 (43.1)	0.0002
	75	> 30 kPa	17 (27.0)	58 (56.9)	
Non-surgical treatment (N = 115)	62	≤ 30 kPa	31 (68.9)	31 (44.3)	0.0098
	53	> 30 kPa	14 (31.1)	39 (55.7)	
Supportive care (N = 32)	11	≤ 30 kPa	5 (71.4)	6 (24.0)	0.0288
	21	> 30 kPa	2 (28.6)	19 (76.0)	
LSM and tumor diameter in the right lobe of the liver					
			Spearman's Correlation Coefficient		p-value
Whole population	135		0.464		< 0.0001
Non-surgical treatment (N = 96)	96		0.446		< 0.0001
Supportive care	28		0.369		0.053

(Abbreviations: ALBI, Albumin-Bilirubin; BCLC, Barcelona Clinic Liver Cancer; LSM, Liver stiffness measurement).

In the current study, it has been observed that LSM in patients receiving systemic therapy or supportive care was higher than the LSM in the surgical cohort. There are two possible explanations. First, patients with more advanced HCC likely have more advanced liver fibrosis, as evidenced by the positive correlations between LSM and BCLC stage as well as the ALBI grade. Second, since the reading of LSM is conducted at the right lobe of the liver, the LSM may be influenced by the presence of a tumor in the right lobe. Amongst patients with tumors in the right lobe of the liver, our data demonstrate that the LSM is correlated with longer tumor diameter in the right lobe. The component of HCC may be stiffer than the liver parenchyma thereby leading to a higher LSM reading. In fact, higher matrix stiffness in HCC is associated with adverse tumor biology via a mechanism of triggering epithelial-mesenchymal transition in HCC cells [17], hence higher LSM may reflect a group of patients with more aggressive biology and worse prognosis.

There are a few limitations of this study. First, hepatitis B viral infection is the predominant etiology of HCC. LSM varies in different etiologies. Similar results and conclusions were observed analyzing the HBV population alone as compared to the whole population. Still, more validation data are required to evaluate whether the results are generalizable to the HCC of other etiologies. Second, a standard methodology of measuring LSM at the right lobe is adopted in the current study [18,19]. Desmoplastic-like reactions could render the tumors stiffer and lead to higher LSM measurements than liver parenchyma. We did not explore another approach to measuring LSM in the left lobe for patients with HCC in the right lobe of the liver. The latter approach may enable measurement of LSM in the non-tumorous part of the liver but will inevitably lead to inconsistency in LSM reading due to the variable position of measurement for each patient. Thirdly, the presence of ascites may impact the accuracy of LSM measurement. Hence, all patients with ascites were excluded from the study. Fourthly, the choice of 30kPa as the cut-off was chosen instead of the median LSM. However, sensitivity analysis using the median LSM of 26.3kPa reveals unaltered results and conclusions. Finally, some pilot studies suggest that liver stiffness may predict the response of immune checkpoint inhibitors in HCC [20]. Our study was unable to analyze this aspect due to the small number of patients receiving immunotherapy (n = 8).

In conclusion, the current study shows that an LSM > 30kPa is a significant adverse predictor of survival for patients with advanced HCC, which is independent of BCLC stage and ALBI grade. Further studies are indicated to validate and evaluate the role of LSM in patients undergoing non-surgical treatment.

Table 4: Univariate analyses on OS.

Variable	*p*-value	Hazard Ratio (HR)	95% CI for HR
Univariable analyses			
Age	0.6521	1.00	0.98–1.01
Sex	0.8378	1.05	0.68–1.60
ECOG	0.0005	1.97	1.35–2.89
History of alcohol	0.1996	0.80	0.56–1.13
HBsAg positive	0.5526	1.13	0.75–1.71
Anti-HCV positive	0.7089	1.12	0.63–1.98
Ascites	0.0008	2.32	1.42–3.78
Symptomatic at presentation	< 0.0001	2.38	1.62–3.50
Vascular invasion	< 0.0001	2.37	1.62–3.46
First-line treatment Supportive care TACE Systemic therapy Surgery	< 0.0001	2.15	1.75–2.64
E Med (kPa) (per SD)	0.0001	1.48	1.25–1.76
Bilirubin	< 0.0001	1.03	1.02–1.04
Albumin	0.0002	0.95	0.92–0.97
ALT	0.0855	1.00	1.00–1.01
ALP	< 0.0001	1.00	1.00–1.00
ln AFP	< 0.0001	1.61	1.43–1.80
Creatinine	0.0581	0.99	0.98–1.00
ALBI	< 0.0001	2.08	1.53–2.84
Child-Pugh score	0.0013	1.95	1.30–2.93
BCLC	< 0.0001	2.05	1.54–2.72
Grouped BCLC (A and B vs C and D)	< 0.0001	2.39	1.64–3.50
Longest tumor diameter	< 0.0001	1.09	1.05–1.12
Longest tumor diameter in the right lobe of the liver	< 0.0001	1.07	1.04–1.11
Tumor number	0.0118	0.62	0.43–0.90

Table 5: Multivariable analyses on OS.

Multivariable analyses			
Model 1			
LSM (E Med) > 30kPa	0.015	1.59	1.10–2.30
ALBI	0.002	1.70	1.22–2.37
ALP	0.001	1.00	1.00–1.00
Model 2			
LSM (E Med) > 30kPa	0.027	1.52	1.05–2.21
BCLC	0.0001	1.72	1.28–2.30
ALP	0.002	1.00	1.00–1.00

(Abbreviations: AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; ALP, alkaline phosphatase; ALT, alanine transaminase; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HBsAg, Hepatitis B surface antigen; Anti-HCV, hepatitis C virus antibody; LSM, liver stiffness measurement; TACE, transarterial chemembolization).

Authors' Contributions

Concept: Stephen L. Chan, Grace L.H. Wong. Collection of data: Stephen L. Chan, Grace L.H. Wong, Leung Li, Yat M. Lau. Statistical analysis: Ka H. Ngai, Frankie Mo, Terry C.F. Yip. Administrative support: Vincent W.S. Wong, Henry L.Y. Chan. Drafting of the manuscript: Ka H. Ngai, Stephen L. Chan, Grace L.H. Wong. Approval of manuscript: Ka H. Ngai, Grace L.H. Wong, Leung Li, Frankie Mo, Yat M. Lau, Kelvin K.C. Ng, Terry C.F. Yip, Vincent W.S. Wong, Henry L.Y. Chan, Stephen L. Chan.

Data Availability

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Funding

No Funding sources for this study.

Ethics Approval

The study was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Research Ethics Committee. There is written informed consent for all patients in this study.

Conflicts of Interest

SLC served as an advisor for Astra-Zeneca, MSD, Eisai, and Ipsen, and received research funding from Bayer, Eisai, SIRTEX, and MSD. GLHW has served as an advisory committee member for Gilead Sciences and Janssen, as a speaker for Abbott, Abbvie, Bristol-Myers Squibb, Echosens, Furui, Gilead Sciences, Janssen, and Roche, and received a research grant from Gilead Sciences. TCFY has served as a speaker and an advisory committee member for Gilead Sciences. HLYC is an advisor for AbbVie, Aligos, Aptorum, Arbutus, Hepion, Janssen, Gilead, GSK, Merck, Roche, Vaccitech, VenatoRx, Vir Biotechnology; and a speaker for Mylan, Gilead, and Roche. VWSW has served as an advisory committee member for AbbVie, Allergan, Echosens, Gilead Sciences, Janssen, Perspectum Diagnostics, Pfizer, and Terns; and a speaker for Bristol-Myers Squibb, Echosens, Gilead Sciences, and Merck.

The other authors declare that they have no competing interests.

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