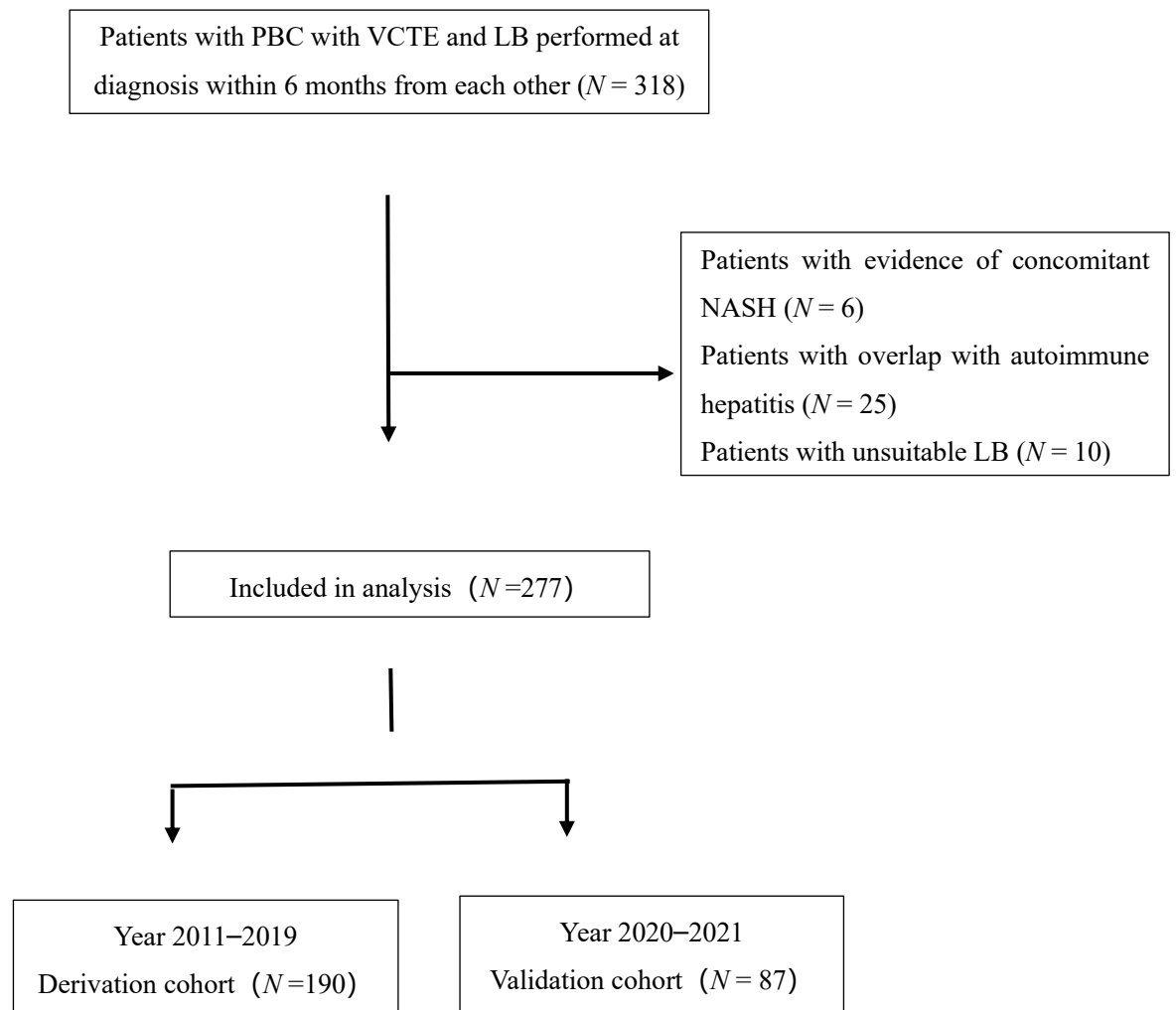
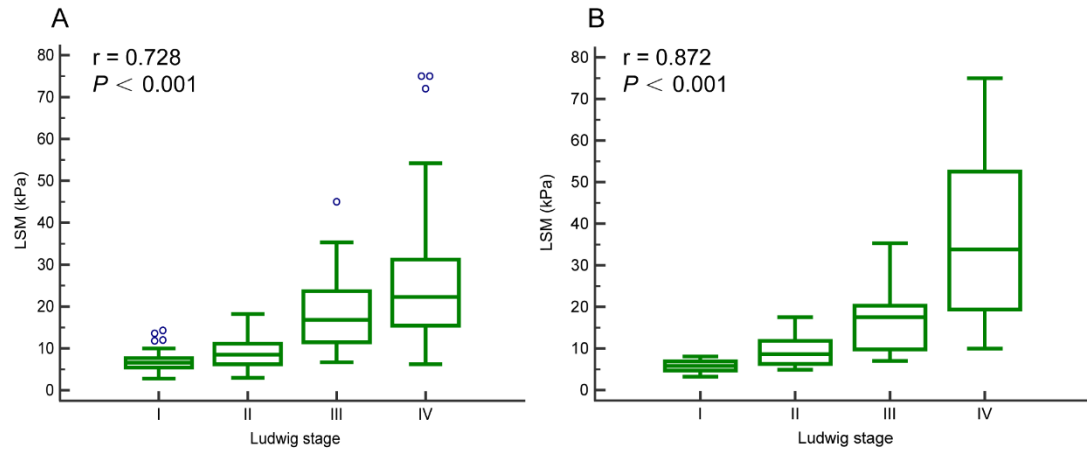


Supplementary Materials



Supplementary Figure S1. Flowchart of patient selection process. PBC, primary biliary cholangitis; VCTE, vibration-controlled transient elastography; NASH, non-alcoholic steatohepatitis; LB, liver biopsy.



Supplementary Figure S2. Distribution of LSM in the derivation (A) and validation (B) cohorts according to Ludwig stage. LSM was positively correlated to histological stage (Spearman correlation test, $P < 0.001$).

Supplementary Table S1 Multivariate analysis of advanced histological stage in the derivation cohort

Variables	Derivation cohort (n = 190)			UDCA treatment-naïve (n = 126)			UDCA-treated (n = 64)	
	OR (95% CI)	<i>P</i> value		OR (95% CI)	<i>P</i> value		OR (95% CI)	<i>P</i> value
LSM (kPa)	1.158 (1.069 – 1.256)	< 0.001		1.102 (1.013 – 1.199)	0.024		2.645 (1.180 – 5.928)	0.018
Age (years)	1.044 (0.980 – 1.111)	0.185		1.078 (0.988 – 1.176)	0.091		0.937 (0.773 – 1.134)	0.503
Female	1.334 (0.237 – 7.505)	0.744		0.624 (0.088 – 4.428)	0.637		7473.324 (0.000 – 1.006e + 33)	0.794
UDCA-naïve	0.264 (0.091 – 0.761)	0.014		—	—		—	—
Diabetes	1.118 (0.179 – 6.981)	0.905		0.841 (0.074 – 9.579)	0.889		3.219 (0.061 – 169.194)	0.563
Hypertension	1.392 (0.364 – 5.330)	0.629		1.316 (0.245 – 7.066)	0.749		0.459 (0.009 – 22.621)	0.695

Total bilirubin (mg/dL)	0.934 1.491	(0.584 - 0.774)	0.846 1.727	(0.415 - 0.647)	5.927 (0.274 - 128.302)	0.257
Albumin (g/dL)	0.518 1.666	(0.161 - 0.270)	0.365 1.629	(0.082 - 0.187)	38.596 (0.244 - 6109.597)	0.157
ALT (×ULN)	0.822 1.433	(0.472 - 0.489)	0.870 1.632	(0.463 - 0.664)	0.451 (0.001 - 154.383)	0.789
AST (×ULN)	1.188 2.086	(0.677 - 0.548)	1.278 2.394	(0.683 - 0.443)	0.014 (0.000 - 230.284)	0.390
ALP (×ULN)	0.757 1.279	(0.448 - 0.298)	0.855 1.550	(0.471 - 0.605)	0.205 (0.008 - 5.326)	0.341
GGT (×ULN)	1.156 1.376	(0.971 - 0.104)	1.167 1.429	(0.953 - 0.135)	0.964 (0.243 - 3.819)	0.959
IgG (g/L)	1.164 1.297	(1.044 - 0.006)	1.138 1.280	(1.011 - 0.032)	1.401 (0.760 - 2.583)	0.280
IgM (g/L)	0.992 1.194	(0.824 - 0.930)	0.987 1.208	(0.807 - 0.901)	1.038 (0.394 - 2.732)	0.940
PLT (×10 ⁹ /L)	0.990 0.998	(0.983 - 0.010)	0.989 0.998	(0.979 - 0.020)	0.991 (0.962 - 1.021)	0.547

AMA positive	0.641	(0.242	-	0.371	0.902	(0.252	-	0.875	0.565	(0.024 - 13.170)	0.722
	1.699)				3.230)						
BMI (kg/m ²)	1.020	(0.870	-	0.812	0.954	(0.771	-	0.662	1.111	(0.854 - 1.445)	0.434
	1.195)				1.179)						

Supplementary Table S2 Tables of predictive values used for the identification of the lower cut-off (10kPa, in bold in Table A) and the higher cut-off (14.5kPa, in bold in Table B) were able to exclude and confirm, the presence of advanced fibrosis, respectively

A

Lower cut-off	Correct positive prediction	Incorrect positive prediction	Correct negative prediction	Incorrect negative prediction	Sensitivity	False negative proportion (1-Sensitivity)	NPV
6.0	78	81	31	0	1 (78/78)	0	1
6.5	77	67	45	1	0.99	0.01	0.98
7.0	76	54	58	2	0.97	0.03	0.97
7.5	76	52	60	2	0.97	0.03	0.97
8.0	75	39	73	3	0.96	0.04	0.96
8.5	74	37	75	4	0.95	0.05	0.95
9.0	72	32	80	6	0.96	0.04	0.93
9.5	72	24	88	6	0.92	0.08	0.94
10.0	71	23	89	7	0.91	0.09	0.93
10.5	69	21	91	9	0.88	0.12	0.91
11.0	68	18	94	10	0.87	0.13	0.90
11.5	63	17	95	15	0.81	0.19	0.86

B

Higher cut-off	Correct positive prediction	Incorrect positive prediction	Correct negative prediction	Incorrect negative prediction	Specificity	False positive proportion (1-Specificity)	PPV
11.0	68	18	94	10	0.84	0.16	0.79
11.5	63	17	95	15	0.85	0.15	0.79

12.0	60	12	100	18	0.89	0.11	0.83
12.5	60	12	100	18	0.89	0.11	0.83
13.0	60	9	103	18	0.92	0.08	0.87
13.5	60	9	103	18	0.92	0.08	0.87
14.0	60	8	104	18	0.93	0.07	0.88
14.5	58	5	107	20	0.96	0.04	0.92
15.0	56	5	107	22	0.96	0.04	0.92
15.5	54	5	107	24	0.96	0.04	0.92
16.0	54	4	108	24	0.96	0.04	0.93
16.5	53	4	108	25	0.96	0.04	0.93
17.0	51	4	108	27	0.96	0.04	0.93
17.5	49	3	109	29	0.97	0.03	0.94
18.0	47	3	109	31	0.97	0.03	0.94
18.5	47	2	110	31	0.98	0.02	0.96
19.0	43	2	110	35	0.98	0.02	0.96

Supplementary Table S3 Area under the ROC curve of advanced stage (Ludwig stage $\geq$ III) with different markers in the derivation and validation cohorts

Markers	Derivation cohort		Validation cohort	
	AUROC (95% CI)	<i>P</i> value (vs. LSM)	AUROC (95% CI)	<i>P</i> value (vs. LSM)
LSM	0.93 (0.88 – 0.96)		0.97 (0.90 – 0.99)	
FIB-4	0.84 (0.78 – 0.89)	0.005	0.88 (0.79 – 0.94)	0.011
APRI	0.75 (0.68 – 0.81)	< 0.001	0.85 (0.76 – 0.92)	0.002
AAR	0.76 (0.69 – 0.82)	< 0.001	0.74 (0.63 – 0.83)	< 0.001
GPR	0.60 (0.53 – 0.67)	< 0.001	0.76 (0.66 – 0.85)	< 0.001
MRS	0.83 (0.76 – 0.88)	< 0.001	0.86 (0.76 – 0.92)	0.001

Supplementary Table S4 Descriptive data of patients values of liver stiffness measurements within the total gray area

Variable	Early stage (n = 22)	Advanced stage (n = 18)	P value
Female, n (%)	18 (81.8)	17 (94.4)	0.230
Age at diagnosis (years)	54 (46 - 61)	51 (47 - 63)	0.817
UDCA-naive, n (%)	10 (45.5)	7 (38.9)	0.676
Comorbidity, n (%)			
Sjogren's syndrome	1 (4.5)	1 (5.6)	1.000
Hashimoto's thyroiditis	3 (13.6)	5 (27.8)	0.430
Diabetes	3 (13.6)	1 (5.6)	0.613
Hypertension	4 (18.2)	4 (22.2)	1.000
Total bilirubin (mg/dL)	0.9 (0.8 - 1.5)	0.8 (0.7 - 1.0)	0.161
Albumin (g/dL)	4.0 (3.8 - 4.4)	3.9 (3.7 - 4.8)	0.754
ALT (×ULN)	1.1 (0.9 - 2.6)	0.7 (0.3 - 0.9)	0.001
AST (×ULN)	1.3 (1.0 - 2.1)	1.1 (0.7 - 1.4)	0.047
ALP (×ULN)	1.7 (1.2 - 2.7)	1.2 (0.9 - 2.1)	0.103
GGT (×ULN)	3.8 (2.6 - 6.8)	1.8 (0.7 - 5.8)	0.036
IgG (g/L)	13.7 (12.2 - 16.2)	16.1 (12.8 - 20.5)	0.178
IgM (g/L)	4.27 (2.10 - 5.37)	2.32 (1.50 - 3.97)	0.128
Platelet count (×10 ⁹ /L)	205 (149 - 244)	161 (77 - 235)	0.219
ANA, n (%)	15 (68.2)	12 (66.7)	0.919
AMA/AMA-M2, n (%)	15 (68.2)	10 (55.6)	0.412
Anti-gp210, n (%)	12 (57.1) ^a	6 (35.3) ^b	0.180
Anti-sp100, n (%)	4 (19.0) ^a	2 (11.8) ^b	0.672
Hyaluronic acid	104.0 (78.6 - 133.7)	93.1 (79.1 - 108.9)	0.482

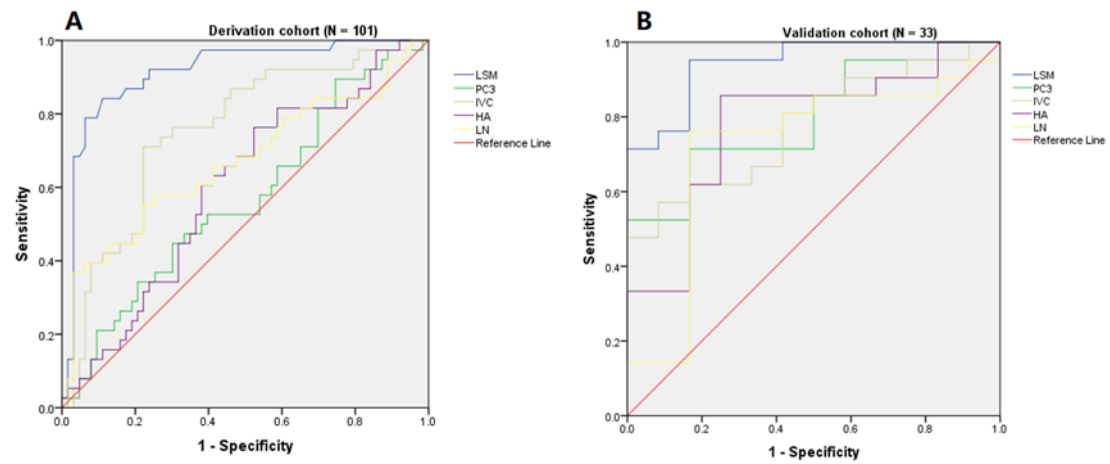
(ng/mL)				
Serum		fibrotic		
markers				
APRI		0.75 (0.48 – 1.10)	0.59 (0.45 – 1.06)	0.399
FIB-4		1.82 (1.44 – 2.66)	2.26 (1.53 – 4.48)	0.232
AAR		0.91 (0.66 – 1.18)	1.29 (0.88 – 1.59)	0.016
GPR		2.68 (1.81 – 5.35)	1.54 (0.84 – 4.24)	0.128
MRS		4.21 (3.86 – 4.48)	4.12 (3.71 – 4.56)	0.703
LSM (kPa)		11.9 (10.9 – 12.8)	11.3 (10.8 – 12.2)	0.369
BMI (kg/m²)		23.3 (18.8 – 24.7)	20.8 (18.8 – 24.4)	0.682

Variables are presented as median (IQR) for continuous variables and total number (%) for categorical variables.

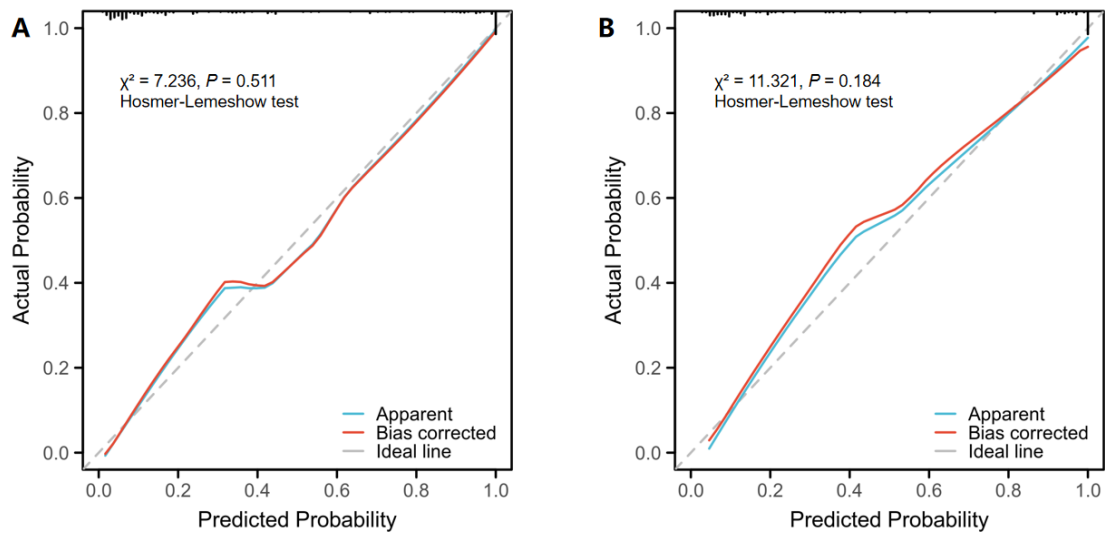
^aAvailable in 21patients.

Supplementary Table S5. Area under the ROC curve of advanced stage (Ludwig stage $\geq$ III) with different serum markers in the derivation and validation cohorts.

Markers	Derivation cohort (n = 101)		Validation cohort (n = 33)	
	AUROC (95% CI)	<i>P</i> value (vs. LSM)	AUROC (95% CI)	<i>P</i> value (vs. LSM)
LSM	0.91 (0.85 – 0.97)		0.94 (0.87 – 1.00)	
PC3	0.57 (0.45 – 0.68)	< 0.001	0.80 (0.65 – 0.95)	< 0.001
IVC	0.76 (0.66 – 0.85)	< 0.001	0.78 (0.62 – 0.934)	< 0.001
HA	0.60 (0.49 – 0.71)	< 0.001	0.78 (0.62 – 0.95)	< 0.001
LN	0.70 (0.55 – 0.79)	< 0.001	0.72 (0.53 – 0.92)	< 0.001



Supplementary Figure S3. Receiver operating characteristic curves of VCTE and serum fibrotic markers for advanced stage (Ludwig III/IV) in derivation (A) and validation (B) cohorts.



Supplementary Figure S4. Calibration curve plots of LSM for diagnosing PBC advanced fibrosis in the derivation (A) and validation cohorts (B). The "Apparent" curve represents the prediction curve, the "Bias-corrected" curve represents the calibration curve, and the "Ideal" curve represents the ideal curve; the closer the curve is to the diagonal line, the better the fitting effect. The Hosmer-Lemeshow Goodness of Fit test is used to evaluate the calibration degree. If $P > 0.05$, it means there is no significant difference between the predicted values and the observed values, so the model has a good fitting degree.

Supplementary Table S6. Area under the ROC curve for diagnosing advanced fibrosis stage (Ludwig stage $\geq$ III) under different UDCA treatment courses in the derivation and validation cohorts.

		Derivation cohort (n = 190)		Validation cohort (n = 87)	
UDCA courses	treatment	N	AUROC (95% CI)	N	AUROC (95% CI)
UDCA naïve	treatment-	126	0.93 (0.88 - 0.98)	46	0.97 (0.93 - 1.00)
	UDCA-treated				
	< 2 years	32	0.90 (0.79-1.00)	20	0.94 (0.84-1.00)
	$\geq$ 2 years	32	0.94 (0.86-1.00)	21	0.97 (0.90 - 1.00)