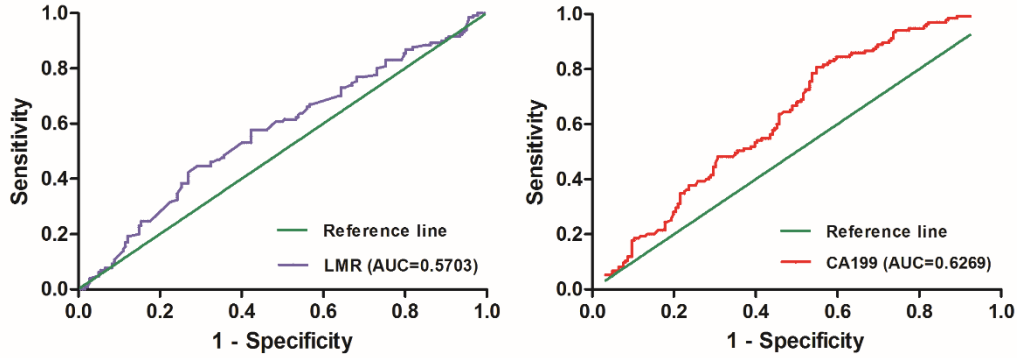


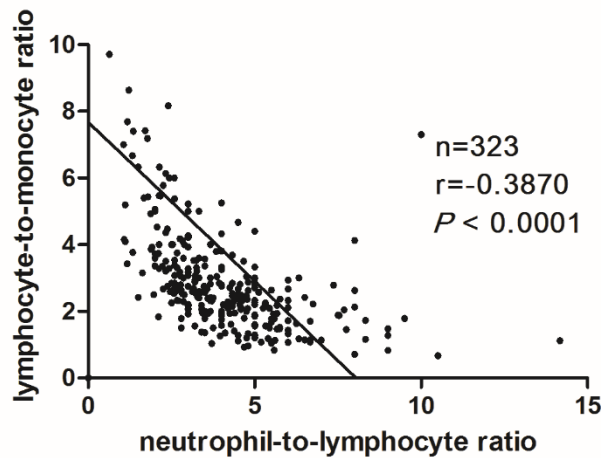
Supplementary file

Supplementary Figures

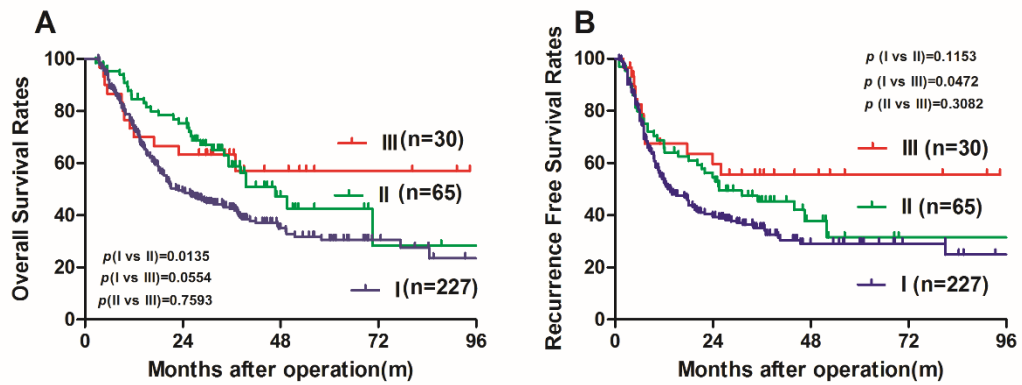


Supplementary Figure 1. Receiver operating characteristics (ROC) curves assessing the cut-off of LMR (left), and CA19-9 (right) for predicting the overall survival in the training cohort (Cohort 1, $n=322$).

The AUCs for each parameter LMR, and CA19-9 were 0.5703 (0.5056-0.6351, $P=0.034$), and 0.6269 (0.5665-0.6873, $P=0.0001$), respectively. LMR=lymphocyte to monocyte ratio, AUC, indicates area under the ROC curve.



Supplementary Figure 2. Negative correlation between lymphocyte-to-monocyte ratio and neutrophil-to-lymphocyte ratio in ICC patients (Cohort 1, $n=322$, $r=-0.3870$, $P < 0.0001$).



Supplementary Figure 3. Prognostic values of prognostic nutritional index (PNI) using Kaplan-Meier analysis (Cohort 1, $n=322$).

Kaplan-Meier analysis for overall survival according to PNI (A). Kaplan-Meier analysis for recurrence-free survival according to PNI (B). The Prognostic Nutritional Index (PNI) was defined as follows: Albumin (g/l) + 5 × lymphocyte count × 10⁹/l ≥ 45, I; Albumin (g/l) + 5 × lymphocyte count × 10⁹/l ≥ 40 & < 45, II; Albumin (g/l) + 5 × lymphocyte count × 10⁹/l < 40, III.

Supplementary Table 1. The clinicopathologic characteristics of ICC patients in the validation cohort

(Cohort 2, n=126)

Clinicopathological Indexes		LMR			CA19-9			SIS			
		low	high	P	low	high	P	I	II	III	P
Age(year)	≤50	21	13	0.895	21	13	0.984	11	12	11	0.287
	>50	58	34		57	35		22	47	23	
Sex	female	24	19	0.250	28	15	0.593	13	21	9	0.509
	male	55	28		50	33		20	38	25	
HBsAg	negative	50	30	0.952	50	30	0.856	21	34	25	0.308
	positive	29	17		28	18		12	25	9	
HCV	negative	78	46	1*	77	47	1*	33	58	33	1*
	positive	1	1		1	1		0	1	1	
AFP (ng/ml)	≤20	72	46	0.256*	73	45	1*	33	53	32	0.177*
	>20	7	1		5	3		0	6	2	
Child-Pugh	A	77	46	1*	77	46	0.557*	33	57	33	0.376*
	B or C	2	1		1	2		0	2	1	
Liver cirrhosis	no	59	33	0.585	56	36	0.694	21	45	26	0.379
	yes	20	14		22	12		12	14	8	
Tumor size (cm)	≤5	36	24	0.550	44	16	0.012	20	31	9	0.012
	>5	43	23		34	32		13	28	25	
Tumor number	single	62	36	0.806	60	38	0.769	24	48	26	0.620
	multiple	17	11		18	10		9	11	8	
Lymphonodus node metastasis	yes	21	5	0.032	10	16	0.006	0	15	11	0.002*
	no	58	42		68	32		33	44	23	
Microvascular invasion	yes	17	9	0.751	14	12	0.342	6	11	9	0.615
	no	62	38		64	36		27	48	25	
Tumor differentiation ^a	poor	22	8	0.212	18	12	0.606	5	16	9	0.293
	moderated	45	27		47	25		19	36	17	
	well	12	12		13	11		9	7	8	
TNM stage ^b	I+II	56	39	0.127	65	30	0.008	31	42	22	0.008*
	III+IVA	23	8		13	18		2	17	12	

Boldface type indicates significant values.

Abbreviations: AFP, alpha-fetoprotein; CA19-9, carbohydrate antigen 19-9; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; LMR, lymphocyte-to-monocyte ratio; TNM, tumor-node-metastasis; SIS, combination of preoperative serum CA19-9 and LMR. I, CA19-9^{Low}/LMR^{High}; II, CA19-9^{High}/LMR^{High} and CA19-9^{Low}/LMR^{Low}; III, CA19-9^{High}/LMR^{Low}.

^a Tumor differentiation was determined according to the “British Society of Gastroenterology guidelines on the management of cholangiocarcinoma”.

^b TNM stage: American Joint Committee on Cancer 7th edition staging for intrahepatic cholangiocarcinoma.

*Fisher's exact tests; chi-square tests for all other analyses.

Supplementary Table 2. Multivariate Cox regression analyses in the validation cohort (Cohort 2, n=126)

Variable	TTR		OS	
	HR (95% CI)	P	HR (95% CI)	P
<i>Univariate analysis</i>				
Age, year (≤50 vs. >50)	0.934 (0.580- 1.504)	0.779	0.813 (0.515- 1.281)	0.372
Sex (female vs. male)	1.516 (0.925- 2.484)	0.099	1.234 (0.768- 1.983)	0.386
HBsAg (negative vs. positive)	1.426 (0.881- 2.307)	0.149	1.618 (1.020- 2.566)	0.041
HCV (negative vs. positive)	0.252 (0.034- 1.853)	0.176	0.197 (0.026- 1.458)	0.112
AFP, ng/ml (≤20 vs. >20)	0.411 (0.146- 1.162)	0.094	0.330 (0.118- 0.917)	0.033
Child-Pugh (A vs. B or C)	0.815 (0.198- 3.352)	0.777	0.411 (0.057- 2.980)	0.379
Liver cirrhosis (no vs. yes)	1.248 (0.748- 2.085)	0.396	1.205 (0.726- 1.999)	0.471
Tumor size, cm (≤5 vs. >5)	1.170 (0.745- 1.837)	0.496	1.189 (0.764- 1.850)	0.443
Tumor number (single vs. multiple)	1.241(0.725- 2.125)	0.431	1.412 (0.842- 2.368)	0.191
Lymphonodus node metastasis (no vs. yes)	2.622 (1.533- 4.484)	0.000	2.634 (1.551- 4.472)	0.000
Microvascular invasion (no vs. yes)	1.469 (0.873- 2.473)	0.148	0.880 (0.501- 1.545)	0.656
Tumor differentiation ^a (P vs. M,W)	1.367 (0.865- 2.160)	0.181	1.017 (0.646- 1.600)	0.943
TNM stage ^b (I+II vs. III+IVA)	2.512 (1.525- 4.138)	0.000	2.360 (1.443- 3.860)	0.001
NLR (low vs. high)	1.618 (1.018- 2.571)	0.042	1.958 (1.232- 3.111)	0.004
LMR (low vs. high)	0.538 (0.327- 0.884)	0.014	0.511 (0.312- 0.837)	0.008
CA19-9, U/ml (≤89 vs. >89)	2.720 (1.669-4.434)	0.000	3.549 (2.222- 5.669)	0.000
SIS				
I	1 (Referent)		1 (Referent)	
II	2.283 (1.207-4.319)	0.011	2.296 (1.182- 4.458)	0.014
III	4.590 (2.268-9.293)	0.000	5.988(3.007-11.925)	0.000
<i>Multivariate analysis¹</i>				
HBsAg (negative vs. positive)	1.030 (0.606- 1.730)	0.931	1.216 (0.738- 2.003)	0.444
HCV (negative vs. positive)	0.299 (0.037- 2.433)	0.259	0.193 (0.024- 1.578)	0.125
Lymphonodus node metastasis (no vs. yes)	0.843 (0.314- 2.263)	0.734	1.807 (1.071- 3.051)	0.027
TNM ^b (I+II vs. III+IVA)	1.944 (1.944- 3.277)	0.013	1.223 (0.453- 3.299)	0.691
NLR (low vs. high)	1.077 (0.638- 1.819)	0.781	1.471 (0.894- 2.421)	0.129
LMR (low vs. high)	0.613 (0.371- 1.013)	0.056	0.465 (0.223- 0.969)	0.041
CA19-9, U/ml (≤89 vs. >89)	2.377 (1.438- 3.932)	0.001	3.115 (1.926- 5.036)	0.000
SIS				
I	1 (Referent)		1 (Referent)	
II	2.083 (1.091- 3.976)	0.026	3.213 (1.365- 7.565)	0.008
III	3.946 (1.913- 8.138)	0.000	9.666 (3.411- 27.394)	0.000

Boldface type indicates significant values.

¹ Analysis including LMR, CA19-9, and SIS.

Analyses were conducted using univariate analysis or multivariate Cox proportional hazards regression.

Abbreviations: AFP, alpha-fetoprotein; CA19-9, carbohydrate antigen 19-9; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; TTR, time to recurrence; OS, overall survival; TNM, tumor-node-metastasis; CI, confidential interval; HR, hazard ratio; P, poor differentiation; M, moderated differentiation; W, well differentiation; SIS, combination of preoperative serum CA19-9 and LMR. I, CA19-9^{Low}/LMR^{High}; II, CA19-9^{High}/LMR^{High} and CA19-9^{Low}/LMR^{Low}; III, CA19-9^{High}/LMR^{Low}.

^a Tumor differentiation was determined according to the “British Society of Gastroenterology guidelines on the management of cholangiocarcinoma”.

^b TNM stage: American Joint Committee on Cancer 7th edition staging for intrahepatic cholangiocarcinoma.