

**Table S1** Source, clone and working dilution of primary antibody

Antibody	Manufacturer	Clone	Dilution
ASCL1	BD Biosciences	24B72D11.1	1:50
NEUROD1	Abcam	EPR17084	1:50
POU2F3	Santa Cruz	6D1	1:25
YAP1	Santa Cruz	63.7	1:150
CD3	Zhongshan Golden Bridge Biotechnology	LN10	1:200
CD8	Zhongshan Golden Bridge Biotechnology	SP16	1:250
CD20	Zhongshan Golden Bridge Biotechnology	L26	1:100
CD68	Zhongshan Golden Bridge Biotechnology	KP1	1:100
CD163	Zhongshan Golden Bridge Biotechnology	10D6	1:100
CD56	Zhongshan Golden Bridge Biotechnology	UMAB83	1:200
Syn	Zhongshan Golden Bridge Biotechnology	27G12	1:200
CgA	Abcam	CGA/414	1:200

Syn, synaptophysin; CgA, chromogranin-A.

**Table S2** Baseline clinicopathologic features

Variables	Subtypes	Number
Age	Median (min–max)	60 (37–80)
Sex	Male	90 (87.4)
	Female	13 (12.6)
Smoking status	Current/former smokers	77 (74.8)
	Never smokers	26 (25.2)
ECOG PS	0–1	103 (100.0)
Stage	I	35 (34.0)
	II	26 (25.2)
	III	32 (31.1)
	IV	10 (9.7)
Chemotherapy	Paclitaxel + platinum	13 (12.6)
	Etoposide + platinum	19 (18.4)
	Pemetrexed + platinum	20 (19.4)
	None	51 (49.6)
Operation	Yes	92 (89.3)
	No	11 (10.7)
Pathological subtypes	Pure	68 (66.0)
	Mixed with NSCLC	25 (24.3)
	Mixed with SCLC	10 (9.7)

Data are presented as n (%) unless otherwise specified. ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

**Table S3** Differences in clinicopathological features among ASCL1 dominant, NEUROD1 dominant and double negative groups

Variables	Subtypes	ASCL1 dominant (N=41)	NEUROD1 dominant (N=15)	Double negative (N=8)	P value
Age, years	≤60	21 (51.2)	7 (46.7)	3 (37.5)	0.87
	>60	20 (48.8)	8 (53.3)	5 (62.5)	
Sex	Male	33 (80.5)	12 (80.0)	8 (100.0)	0.55
	Female	8 (19.5)	3 (20.0)	0 (0.0)	
Smoking status	No	12 (29.3)	5 (33.3)	1 (12.5)	0.60
	Current or ever smokers	29 (70.7)	10 (66.7)	7 (87.5)	
EGOG-PS	0-1	41 (100.0)	15 (100.0)	8 (100.0)	/
CD56	Negative	5 (12.2)	5 (33.3)	4 (50.0)	0.03*
	Positive	36 (87.8)	10 (66.7)	4 (50.0)	
Syn	Negative	4 (9.8)	0 (0.0)	4 (50.0)	0.007*
	Positive	37 (90.2)	15 (100.0)	4 (50.0)	
CgA	Negative	15 (36.6)	5 (33.3)	6 (75.0)	0.12
	Positive	29 (63.4)	10 (66.7)	2 (25.0)	
Tumor stage	I	11 (26.8)	6 (40.0)	4 (50.0)	0.78
	II	15 (36.6)	4 (26.7)	1 (12.5)	
	III	12 (29.3)	4 (26.7)	3 (37.5)	
	IV	3 (7.3)	1 (6.7)	0 (0.0)	
Pathological classification	Pure	26 (63.4)	10 (66.7)	7 (87.5)	0.86
	Mixed with NSCLC	10 (24.4)	3 (20.0)	1 (12.5)	
	Mixed with SCLC	5 (12.2)	2 (13.3)	0 (0.0)	
Chemotherapy regimens	Paclitaxel + platinum	5 (12.2)	2 (13.3)	0 (0.0)	0.95
	Etoposide + platinum	5 (12.2)	2 (13.3)	2 (25.0)	
	Pemetrexed + platinum	9 (22.0)	3 (20.0)	1 (12.5)	
	None	22 (53.7)	8 (53.3)	5 (62.5)	

Data are presented as n (%). The Fisher exact test was used to calculate the correlations between clinicopathological features among different groups. \*, statistically significance (P<0.05). ECOG-PS, Eastern Cooperative Oncology Group Performance Status; Syn, synaptophysin; CgA, chromogranin-A; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

**Table S4** Correlation between systematic inflammation indexes and clinical characteristics in lung LCNEC

Variables	Subtypes	LMR			NLR			PLR			SII		
		≤3.3 (N=35)	>3.3 (N=68)	P value	≤2.9 (N=67)	>2.9 (N=36)	P value	≤95.4 (N=18)	>95.4 (N=85)	P value	≤530.8 (N=34)	>530.8 (N=69)	P value
Age, years	≤60	15 (42.9)	37 (54.4)	0.27 <sup>a</sup>	32 (47.8)	20 (55.6)	0.45 <sup>a</sup>	11 (61.1)	41 (48.2)	0.32 <sup>a</sup>	16 (47.1)	36 (52.2)	0.63 <sup>a</sup>
	>60	20 (57.1)	31 (45.6)		35 (52.2)	16 (44.4)		7 (38.9)	44 (51.8)		18 (52.9)	33 (47.8)	
Sex	Male	34 (97.1)	56 (82.4)	0.07 <sup>b</sup>	59 (88.1)	31 (86.1)	0.78 <sup>b</sup>	17 (94.4)	73 (85.9)	0.55 <sup>c</sup>	29 (85.3)	61 (88.4)	0.90 <sup>a</sup>
	Female	1 (2.9)	12 (17.6)		8 (11.9)	5 (13.9)		1 (5.6)	12 (14.1)		5 (14.7)	8 (11.6)	
Smoking status	Current/ever smokers	30 (85.7)	47 (69.1)	0.07 <sup>a</sup>	50 (74.6)	27 (75.0)	0.97 <sup>a</sup>	14 (77.8)	63 (74.1)	0.98 <sup>b</sup>	24 (70.6)	53 (76.8)	0.49 <sup>a</sup>
	Never smokers	5 (14.3)	21 (30.9)		17 (25.4)	9 (25.0)		4 (22.2)	22 (25.9)		10 (29.4)	16 (23.2)	
ECOG PS	0-1	35 (100.0)	68 (100.0)	/	67 (100.0)	36 (100.0)	/	18 (100.0)	85 (100.0)	/	34 (100.0)	69 (100.0)	/
Tumor stage	I	10 (28.6)	25 (36.8)	0.85 <sup>b</sup>	23 (34.3)	12 (33.3)	0.92 <sup>b</sup>	5 (27.8)	30 (35.3)	0.64 <sup>c</sup>	10 (29.4)	25 (36.2)	0.69 <sup>b</sup>
	II	9 (25.7)	17 (25.0)		16 (23.9)	10 (27.8)		4 (22.2)	22 (25.9)		10 (29.4)	16 (23.2)	
	III	12 (34.3)	20 (29.4)		22 (32.8)	10 (27.8)		8 (44.4)	24 (28.2)		12 (35.3)	20 (29.0)	
	IV	4 (11.4)	6 (8.8)		6 (9.0)	4 (11.1)		1 (5.6)	9 (10.6)		2 (5.9)	8 (11.6)	
Pathological classification	Pure	22 (62.9)	46 (67.6)	0.35 <sup>c</sup>	42 (62.7)	26 (72.2)	0.06 <sup>c</sup>	15 (83.3)	53 (62.4)	0.10 <sup>c</sup>	25 (73.5)	43 (62.3)	0.62 <sup>b</sup>
	Mixed with NSCLC	11 (31.4)	14 (20.6)		15 (22.3)	10 (27.8)		1 (5.6)	24 (28.2)		6 (17.6)	19 (27.5)	
	Mixed with SCLC	2 (5.7)	8 (11.8)		0 (0.0)	10 (100.0)		2 (11.1)	8 (9.4)		3 (8.8)	7 (10.1)	
Chemotherapy regimens	Paclitaxel + platinum	3 (8.6)	10 (14.7)	0.79 <sup>b</sup>	8 (11.9)	5 (13.9)	0.82 <sup>a</sup>	2 (11.1)	11 (12.9)	0.96 <sup>b</sup>	5 (14.7)	8 (11.6)	0.22 <sup>b</sup>
	Etoposide + platinum	6 (17.1)	13 (19.1)		14 (20.9)	5 (13.9)		3 (16.7)	16 (18.8)		6 (17.6)	13 (18.8)	
	Pemetrexed + platinum	7 (20.0)	13 (19.1)		12 (17.9)	8 (22.2)		3 (16.7)	17 (20.0)		3 (15.0)	17 (24.6)	
	None	19 (54.3)	32 (47.1)		33 (49.3)	18 (50.0)		10 (55.6)	41 (48.2)		20 (58.8)	31 (44.9)	
Operation	No	7 (25.0)	4 (5.9)	0.06 <sup>b</sup>	5 (7.5)	6 (16.7)	0.27 <sup>a</sup>	1 (5.6)	10 (11.8)	0.72 <sup>c</sup>	1 (2.9)	10 (14.5)	0.15 <sup>c</sup>
	Yes	28 (75.0)	64 (94.1)		62 (92.5)	30 (83.3)		17 (94.4)	75 (88.2)		33 (97.1)	59 (85.5)	
BMI	Mean ± SD	22.0±3.0	22.7±2.9	0.70 <sup>d</sup>	22.6±2.6	22.2±3.6	0.57 <sup>d</sup>	22.6±2.5	22.5±3.0	0.89 <sup>d</sup>	22.7±2.7	22.4±3.1	0.55 <sup>d</sup>
Blood indexes (mean ± SD)	CRP (mg/L)	25.4±40.3	8.1±14.6	0.004 <sup>*a</sup>	8.4±14.2	24.4±40.4	0.09 <sup>e</sup>	6.8±11.5	15.5±29.5	0.18 <sup>e</sup>	5.4±8.8	18.2±32.1	0.02 <sup>*a</sup>
	LDH (U/L)	221.4±130.0	198.8±63.8	0.91 <sup>e</sup>	193.7±65.6	238.6±143.4	0.07 <sup>e</sup>	206.0±91.8	210.1±103.9	0.85 <sup>e</sup>	195.5±75.5	216.2±112.0	0.26 <sup>e</sup>
	ALB (g/L)	40.0±5.2	43.0±3.1	0.005 <sup>*a</sup>	42.5±2.9	40.9±5.7	0.26 <sup>e</sup>	42.1±2.9	41.9±4.4	0.88 <sup>e</sup>	42.3±2.7	41.8±4.7	0.95 <sup>e</sup>

Data are presented as n (%) unless otherwise specified. The superscripts indicate the statistical methods used in the analysis: <sup>a</sup>, Chi-square test; <sup>b</sup>, continuity correction; <sup>c</sup>, Fisher's exact test; <sup>d</sup>, two independent sample t-test; <sup>e</sup>, Mann-Whitney test. \*, statistically significance (P<0.05). LMR, lymphocyte and monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; BMI, body mass index; CRP, C-reactive protein; LDH, lactate dehydrogenase; ALB, albumin; SD, standard deviation.

**Table S5** Counts of intra-tumoral and stromal infiltrating immune cells

Variables	Mean ± SD	Range
Intra-tumoral infiltrating immune cells (cells/mm <sup>2</sup> )		
CD3 <sup>+</sup>	1224±1477	70-6070
CD8 <sup>+</sup>	895±1185	30-5370
CD20 <sup>+</sup>	1224±377	0-1520
CD68 <sup>+</sup>	579±341	60-1590
CD163 <sup>+</sup>	292±195	0-790
Stromal infiltrating immune cells (cells/mm <sup>2</sup> )		
CD3 <sup>+</sup>	2540±862	930-5280
CD8 <sup>+</sup>	1795±856	490-4400
CD20 <sup>+</sup>	518±396	100-1820
CD68 <sup>+</sup>	1699±435	840-2970
CD163 <sup>+</sup>	1224±377	350-2840

SD, standard deviation.

**Table S6** The difference of the tissue TIL/TIM status between groups stratified by LMR, NLR, PLR or SII (mean ± SD)

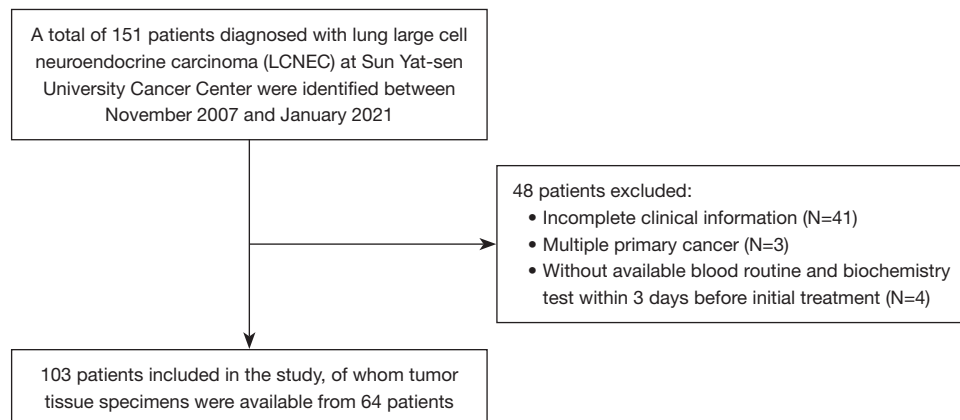
Variables	LMR			NLR			PLR			SII		
	≤3.3	>3.3	P value	≤2.9	>2.9	P value	≤95.4	>95.4	P value	≤530.8	>530.8	P value
Intra-tumoral TIL/TIM												
CD3 <sup>+</sup> cells	641±685	1508±1672	0.004 <sup>b*</sup>	1284±1571	1099±1291	0.79 <sup>b</sup>	1599±1810	1128±1385	0.48 <sup>b</sup>	1362±1416	1129±1529	0.21 <sup>b</sup>
CD8 <sup>+</sup> cells	484±618	1096±1342	0.01 <sup>b*</sup>	893±1176	900±1234	0.97 <sup>b</sup>	1205±1474	816±1104	0.46 <sup>b</sup>	968±1161	846±1214	0.36 <sup>b</sup>
CD20 <sup>+</sup> cells	128±146	190±269	0.24 <sup>b</sup>	187±270	132±143	0.42 <sup>b</sup>	180±260	166±233	0.85 <sup>b</sup>	170±198	168±262	0.40 <sup>b</sup>
CD68 <sup>+</sup> cells	398±153	667±373	<0.001 <sup>a*</sup>	590±367	556±289	0.88 <sup>b</sup>	559±449	584±314	0.40 <sup>b</sup>	601±383	563±314	0.84 <sup>b</sup>
CD163 <sup>+</sup> cells	239±151	318±210	0.19 <sup>b</sup>	276±193	324±201	0.40 <sup>b</sup>	278±224	296±190	0.77 <sup>a</sup>	305±196	283±197	0.63 <sup>b</sup>
Stromal TIL/TIM												
CD3 <sup>+</sup> cells	2492±767	2563±913	0.76 <sup>a</sup>	2549±793	2522±1011	0.91 <sup>a</sup>	2724±793	2493±880	0.39 <sup>a</sup>	2667±859	2453±865	0.33 <sup>a</sup>
CD8 <sup>+</sup> cells	1841±751	1772±910	0.50 <sup>b</sup>	1741±811	1904±952	0.48 <sup>a</sup>	1788±755	1797±886	0.98 <sup>a</sup>	1783±922	1803±820	0.93 <sup>a</sup>
CD20 <sup>+</sup> cells	499±301	527±438	0.70 <sup>b</sup>	523±393	507±412	0.88 <sup>b</sup>	508±447	520±387	0.65 <sup>b</sup>	552±427	494±378	0.48 <sup>b</sup>
CD68 <sup>+</sup> cells	1597±368	1698±434	0.46 <sup>a</sup>	1750±458	1594±373	0.18 <sup>a</sup>	1817±410	1669±440	0.25 <sup>b</sup>	1745±401	1667±459	0.45 <sup>b</sup>
CD163 <sup>+</sup> cells	1118±407	1276±355	0.12 <sup>a</sup>	1282±394	1107±318	0.08 <sup>a</sup>	1359±315	1190±387	0.15 <sup>a</sup>	1310±306	1166±412	0.13 <sup>a</sup>

The superscript "a" indicates two independent sample *t*-test, the superscript "b" indicates Mann-Whitney test. \*, statistically significance (P<0.05). LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; TIL, tumor infiltrating lymphocyte; TIM, tumor infiltrating macrophage.

**Table S7** Differences in inflammatory indicators and tissue TIL/TIM status among ASCL1 dominant, NEUROD1 dominant and double negative groups (mean  $\pm$  SD)

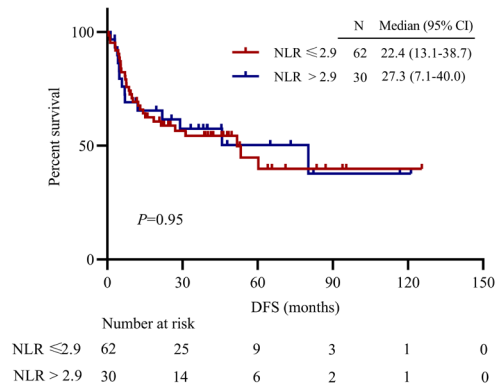
Variables	ASCL1 dominant (N=41)	NEUROD1 dominant (N=15)	Double negative (N=8)	P value
LMR	4.4 $\pm$ 1.9	3.6 $\pm$ 1.6	3.7 $\pm$ 1.1	0.30 <sup>b</sup>
NLR	3.1 $\pm$ 2.7	4.6 $\pm$ 7.5	1.8 $\pm$ 0.5	0.15 <sup>b</sup>
PLR	149.4 $\pm$ 107.5	168.9 $\pm$ 121.7	130.0 $\pm$ 63.5	0.74 <sup>b</sup>
SII	846.6 $\pm$ 796.4	1091.5 $\pm$ 1684.9	508.8 $\pm$ 307.6	0.32 <sup>b</sup>
Intra-tumoral TIL/TIM				
CD3 <sup>+</sup> cells	1217 $\pm$ 1498	1452 $\pm$ 1702	826 $\pm$ 859	0.74 <sup>b</sup>
CD8 <sup>+</sup> cells	916 $\pm$ 1276	1051 $\pm$ 1205	498 $\pm$ 442	0.84 <sup>a</sup>
CD20 <sup>+</sup> cells	179 $\pm$ 253	183 $\pm$ 254	96 $\pm$ 37	0.78 <sup>b</sup>
CD68 <sup>+</sup> cells	538 $\pm$ 284	647 $\pm$ 447	660 $\pm$ 402	0.45 <sup>a</sup>
CD163 <sup>+</sup> cells	294 $\pm$ 210	255 $\pm$ 139	351 $\pm$ 211	0.53 <sup>a</sup>
Stromal TIL/TIM				
CD3 <sup>+</sup> cells	2444 $\pm$ 830	2797 $\pm$ 1047	2553 $\pm$ 606	0.40 <sup>b</sup>
CD8 <sup>+</sup> cells	1692 $\pm$ 857	2010 $\pm$ 915	1918 $\pm$ 734	0.35 <sup>b</sup>
CD20 <sup>+</sup> cells	507 $\pm$ 364	581 $\pm$ 539	454 $\pm$ 244	0.98 <sup>b</sup>
CD68 <sup>+</sup> cells	1750 $\pm$ 452	1520 $\pm$ 320	1773 $\pm$ 475	0.19 <sup>a</sup>
CD163 <sup>+</sup> cells	1240 $\pm$ 388	1129 $\pm$ 333	1322 $\pm$ 405	0.46 <sup>a</sup>

The superscript “a” indicates one way ANOVA test, the superscript “b” indicates Kruskal-Wallis test. LMR, lymphocyte and monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; TIL, tumor-infiltrating lymphocyte; TIM, tumor infiltrating macrophage.

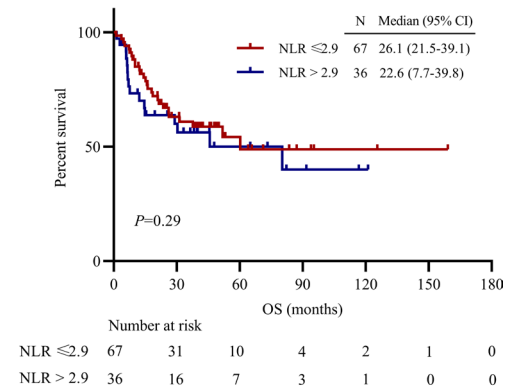


**Figure S1** Study flow diagram.

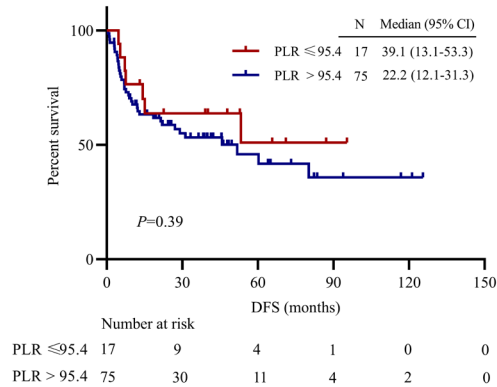
A



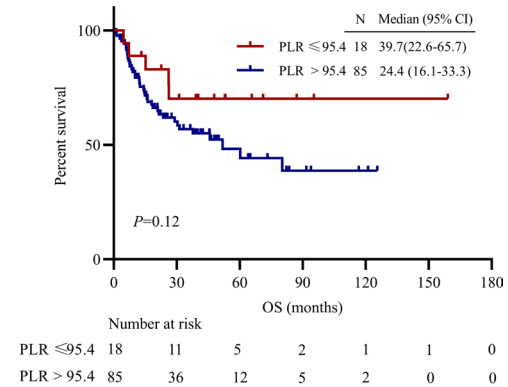
B



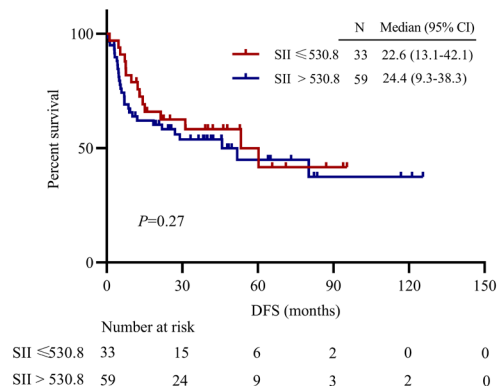
C



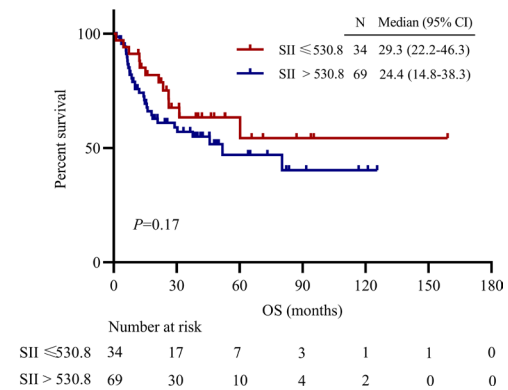
D



E



F



**Figure S2** Kaplan-Meier survival curves of DFS and OS. DFS (A) and OS (B) in patients with low NLR ( $\leq 2.9$ ) versus patients with high NLR ( $> 2.9$ ). DFS (C) and OS (D) in patients with low PLR ( $\leq 95.4$ ) versus patients with high PLR ( $> 95.4$ ). DFS (E) and OS (F) in patients with low SII ( $\leq 530.8$ ) versus patients with high SII ( $> 530.8$ ). Statistical significance was calculated by Kaplan-Meier method with log-rank test. A two-sides of  $P < 0.05$  was considered significant. The number and median survival time (with 95% confidence interval) of patients in each group are indicated. DFS, disease-free survival; OS, overall survival; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.