

Table S1. The definitions of systemic inflammation indices.

Abbreviation	Indicators	Formula
NLR	Neutrophil-to-lymphocyte ratio	Neutrophil count / Lymphocyte count
LMR	Lymphocyte-to-monocyte ratio	Lymphocyte count / Monocyte count
PLR	Platelet-to-lymphocyte ratio	Platelet count / Lymphocyte count
ALI	Advanced lung cancer inflammation index	$BMI \times Albumin (g/L) / NLR$
SII	Systemic immune-inflammation index	$Platelet\ count \times NLR$
SIRI	Systemic inflammation response index	$Neutrophil\ count \times Monocyte\ count / Lymphocyte\ count$
PNI	Prognostic nutritional index	$Albumin (g/L) + 5 \times Lymphocyte\ count (10^9/L)$

Table S2. Baseline hematological parameters of the entire cohort.

Blood index	Median	IQR	Blood index	Median	IQR
IFN- α	1.0	0.4-1.9	NLR	3.5	2.5-4.6
IFN- γ	2.2	1.1-4.6	LMR	3.0	2.3-3.8
IL-4	1.1	0.8-2.1	PLR	173.8	132.2-239.2
IL-5	2.3	1.4-3.5	SII	776.8	502.2-1305.0
IL-17	2.6	0.8-5.6	SIRI	1.4	1.0-2.5
IL-12	1.2	0.8-1.8	ALI	240.0	170.9-356.3
IL-6	8.5	4.4-26.6	PNI	43.7	40.4-46.4
IL-8	10.2	0.0-46.3	LDH	247.0	190.5-323.8
IL-10	1.6	1.1-2.8	RDW	12.8	12.5-13.3
IL-1 β	2.3	0.4-5.1	CRP	8.0	2.3-33.8
TNF- α	2.0	0.8-3.3			

NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; ALI, advanced lung cancer inflammation index; PNI, prognostic nutrition index; IQR, interquartile range.

Table S3. Differences in baseline cytokine levels across different clinical characteristics.

Characteristics		IFN- α	IFN- γ	IL-4	IL-5	IL-17	IL-12	IL-6	IL-8	IL-10	IL-1 β	TNF- α
Age group	< 65	1.0	1.9	1.3	2.7	2.7	1.3	10.4	6.3	1.4	1.3	2.0
		(0.4,	(1.1,	(0.9,	(1.8,	(1.5,	(0.8,	(4.3,	(0,	(1.1,	(0,	(0.8,
		1.6)	4.6)	1.8)	4.0)	5.3)	1.7)	23.2)	39.0)	2.0)	3.5)	3.1)
	≥ 65	1.0	2.6	1.1	2.2	2.5	1.2	7.9	15.0	1.8	3.3	2.1

		(0.6, 2.5)	(0.8, 4.4)	(0.8, 2.1)	(1.3, 3.3)	(0.2, 5.6)	(0.8, 2.0)	(4.6, 27.5)	(0, 46.6)	(1.2, 3.2)	(1.8, 5.6)	(0.9, 3.4)
	<i>P</i>									0.023	0.007	
Gender	Female	0.8	2.1	1.6	1.8	1.7	1.0	9.1	11.8	1.5	2.2	2.7
		(0.4, 1.3)	(1.1, 3.8)	(0.9, 2.1)	(1.5, 2.2)	(0.4, 2.2)	(0.7, 2.0)	(4.1, 16.2)	(1.8, 38.4)	(1.2, 2.2)	(0.5, 3.9)	(1.1, 4.1)
	Male	1	2.2	1.1	2.5	2.7	1.3	8.5	10.2	1.6	2.3	2.0
		(0.5, 1.9)	(1.1, 4.6)	(0.8, 1.8)	(1.5, 3.7)	(0.9, 5.7)	(0.8, 1.8)	(4.6, 26.6)	(0, 48.1)	(1.1, 2.8)	(0.5, 5.4)	(0.8, 3.2)
	<i>P</i>					0.046						
Smoking history	Never	1.1	2.6	1.2	2	1.8	1.1	4.7	4.5	1.5	2.2	2.0
		(0.4, 1.6)	(0.9, 4.5)	(0.8, 2.1)	(1.6, 2.3)	(0, 4.0)	(0.9, 1.9)	(2.7, 11.0)	(0.4, 21.6)	(1.2, 2.5)	(0.5, 4.1)	(1.0, 3.4)
	Former /current	1.0	2.1	1.1	2.6	2.7	1.3	9.6	9.9	1.6	2.3	2 (0.9, 3.0)
		(0.5, 2.0)	(1.1, 4.4)	(0.8, 2.0)	(1.3, 3.8)	(0.9, 5.7)	(0.8, 1.8)	(4.9, 26.7)	(0, 49.3)	(1.2, 2.7)	(0.6, 5.4)	
	<i>P</i>							0.029				
Disease stage	III	1.1	2.8	1.1	2.5	1.4	0.8	5.6	3.4	1.4	2.2	1.7
		(0.7, 1.5)	(1.0, 5.5)	(0.7, 1.7)	(1.6, 4.2)	(0, 3.5)	(0.6, 1.2)	(3.5, 7.5)	(1.1, 40.2)	(1.1, 2.7)	(0, 5.1)	(0.9, 2.9)
	IV	1	2.2	1.1	2.3	2.7	1.4	11.1	10.3	1.6	2.3	2.0
		(0.4, 1.9)	(1.1, 4.4)	(0.9, 2.1)	(1.4, 3.5)	(1.2, 5.6)	(0.8, 1.9)	(4.6, 28.1)	(0, 49.3)	(1.1, 2.7)	(0.6, 4.5)	(0.8, 3.4)
	<i>P</i>											
ECOG PS	0-1	1.0	2.2	1.1	2.3	2.6	1.2	7.5	9.6	1.6	2.3	1.8
		(0.5, 1.9)	(1.0, 4.8)	(0.8, 2.1)	(1.4, 3.7)	(0.8, 5.4)	(0.7, 1.8)	(4.3, 20.8)	(0, 40.4)	(1.1, 2.6)	(0.2, 4.2)	(0.8, 3.3)
	≥2	1	1.8	1.1	2.5	3.0	1.5	23.6	22.2	1.9	4.3	2.7
		(0.5, 2.1)	(1.1, 2.7)	(0.9, 1.9)	(2.1, 2.8)	(2.4, 6.5)	(1.0, 1.9)	(9.6, 52.5)	(0.1, 52.7)	(1.3, 2.8)	(1.6, 11.8)	(1.6, 3.5)
	<i>P</i>											
PD-L1 TPS	<1%	1.2	2.7	1.2	2.5	2.5	1.1	8.2	9.6	1.5	2.1	2.0
		(0.4, 1.9)	(1.3, 4.7)	(0.9, 2.1)	(1.3, 3.3)	(1.3, 5.5)	(0.6, 1.7)	(4.6, 26.7)	(0, 36.9)	(1.1, 2.5)	(0, 4.7)	(0.8, 3.3)
	≥1%	0.7	1.7	1	2.4	1.3	1.3	5.5	8.9	1.8	2.1	2.6
		(0.5, 1.2)	(0.7, 3.6)	(0.7, 1.8)	(1.7, 3.7)	(0, 4.9)	(0.6, 2.0)	(2.5, 22.1)	(0, 41.6)	(1.2, 2.9)	(0.7, 3.4)	(0.1, 3.0)
	<i>P</i>											
Brain metastases	No	0.9	2.1	1.1	2.5	2.5	1.2	7.6	9.6	1.6	2.3	2 (0.9, 3.4)
		(0.4, 1.6)	(1.1, 4.7)	(0.8, 1.8)	(1.8, 3.6)	(0.6, 5.0)	(0.6, 1.8)	(3.5, 23.4)	(0, 42.5)	(1.1, 2.8)	(0.6, 4.6)	
	Yes	1.3	2.7	1.1	2	3.1	1.3	11.0	15 (0, 52.7)	1.7	2.2	1.6
		(0.7, 2.1)	(1.1, 3.8)	(0.9, 2.2)	(0.9, 3.1)	(1.7, 6.0)	(0.9, 1.9)	(5.0, 27.4)		(1.1, 2.2)	(0.3, 5.5)	(0.8, 3.0)

		<i>P</i>											
Liver metastases	No	1.0	2.0	1.1	2.3	2.6	1.1	7.9	7.8	1.5	2.1	1.8	
		(0.4, 1.6)	(1.0, 3.8)	(0.8, 1.6)	(1.5, 3.4)	(0.8, 5.3)	(0.6, 1.7)	(3.5, 21.7)	(0, 30.4)	(1.1, 2.3)	(0, 3.8)	(0.3, 3.3)	
	Yes	1.4	3.5	2.2	2.4	2.7	1.6	13.3	45.2	2.2	5.4	2.3	
		(0.7, 2.6)	(1.8, 5.0)	(1.0, 2.5)	(1.5, 3.8)	(1.4, 6.8)	(1.2, 2.2)	(6.0, 27.9)	(15.7, 99.7)	(1.8, 4.1)	(2.3, 11.0)	(1.3, 3.3)	
		<i>P</i>			0.022			0.005		0.002		0.003	0.002
Bone metastases	No	0.9	2.2	1.0	2.1	2.4	1.1	6.8	9.6	1.5	2.2	1.4	
		(0.4, 1.5)	(0.8, 4.7)	(0.7, 1.6)	(1.3, 3.2)	(0.4, 5.2)	(0.6, 1.7)	(4.1, 16.3)	(0, 38.4)	(1.1, 2.3)	(0.4, 3.9)	(0.3, 3.0)	
	Yes	1.3	2.3	1.7	2.8	3.9	1.6	20.5	13.9	1.9	3.3	2.5	
		(0.7, 2.6)	(1.5, 4.1)	(1.0, 2.4)	(2.2, 3.9)	(2.5, 5.7)	(1.0, 2.1)	(6.5, 33.6)	(0, 50.6)	(1.3, 3.2)	(1.5, 8.5)	(1.6, 4.7)	
		<i>P</i>			0.009			0.035	0.031	0.019		0.006	
Number of metastatic sites	<3	0.9	2.1	1.1	2.3	2.5	1.1	7.7	9.0	1.5	2.2	1.9	
		(0.4, 1.6)	(0.8, 4.0)	(0.8, 1.7)	(1.5, 3.5)	(0.8, 5.4)	(0.7, 1.8)	(3.8, 28.8)	(0, 40.2)	(1.1, 2.4)	(0.3, 3.8)	(0.7, 3.3)	
	≥3	1.8	3.5	2.1	2.7	2.8	1.5	12.2	23.3	1.9	6.0	2.5	
		(0.7, 2.5)	(2.1, 8.3)	(0.8, 2.5)	(1.4, 3.8)	(1.6, 10.1)	(1.0, 2.0)	(6.7, 22.7)	(11.7, 52.9)	(1.5, 3.6)	(3.1, 11.9)	(1.5, 3.1)	
		<i>P</i>			0.029			0.037		0.020	0.004		

Data are presented as median (IQR). IQR, interquartile range.

Table S4. Optimal cutpoint determination of baseline hematological parameters based on PFS or OS.

Blood index	Cutpoint	
	Based on PFS	Based on OS
IFN- α	1.2	2.6
IFN- γ	2.1	2.1
IL-4	0.2	2.3
IL-5	1.3	2.5
IL-17	0.9	1.0
IL-12	0.4	0.4
IL-6	5.0	35.9
IL-8	10.1	9.6
IL-10	2.6	1.0
IL-1 β	5.1	1.9
TNF- α	3.4	4.3
NLR	1.9	4.1
LMR	3.1	3.1
PLR	101	145.1

regimens						
PD-1	1			1		
PD-L1	0.79	0.46-1.36	0.3940	0.90	0.49-1.65	0.7270
IFN-α						
Low	1			1		
High	1.85	1.11-3.09	0.0185	3.04	1.38-6.68	0.0056
IFN-γ						
Low	1			1		
High	2.09	1.27-3.45	0.0038	2.49	1.45-4.27	0.0009
IL-4						
Low	1			1		
High	2.38	0.86-6.58	0.0958	1.95	1.00-3.79	0.0496
IL-5						
Low	1			1		
High	0.59	0.35-0.98	0.0433	0.59	0.34-1.03	0.0616
IL-17						
Low	1			1		
High	1.69	0.97-2.94	0.0667	1.71	0.92-3.18	0.0930
IL-12						
Low	1			1		
High	2.59	1.11-6.06	0.0279	2.62	1.03-6.68	0.0437
IL-6						
Low	1			1		
High	1.82	1.06-3.11	0.0294	2.57	1.30-5.08	0.0066
IL-8						
Low	1			1		
High	1.93	1.19-3.13	0.0076	1.89	1.13-3.16	0.0157
IL-10						
Low	1			1		
High	2.00	1.18-3.39	0.0095	2.57	1.28-5.17	0.0079
IL-1β						
Low	1			1		
High	2.06	1.22-3.48	0.0071	2.00	1.17-3.41	0.0111
TNF-α						
Low	1			1		
High	2.34	1.33-4.11	0.0032	4.79	2.29-10.00	<0.0001
NLR						
Low	1			1		
High	3.10	1.30-7.39	0.0107	2.16	1.29-3.62	0.0036
LMR						
Low	1			1		
High	0.37	0.23-0.62	0.0001	0.45	0.26-0.75	0.0024
PLR						
Low	1			1		

High	2.23	1.00-5.00	0.0508	1.68	0.98-2.87	0.0584
SII						
Low	1			1		
High	1.71	1.02-2.87	0.0410	1.56	0.94-2.60	0.0879
SIRI						
Low	1			1		
High	1.83	1.09-3.08	0.0230	2.56	1.47-4.45	0.0009
ALI						
Low	1			1		
High	0.28	0.11-0.73	0.0090	0.40	0.23-0.69	0.0010
PNI						
Low	1			1		
High	0.37	0.16-0.88	0.0236	0.44	0.21-0.93	0.0320
LDH						
≤ULN	1			1		
>ULN	1.68	1.05-2.69	0.0299	2.43	1.44-4.09	0.0008
RDW						
≤ULN	1			1		
>ULN	3.12	1.51-6.45	0.0022	2.63	1.24-5.61	0.0120
CRP	1.00	0.99-1.01	0.1010	1.01	1.00-1.01	0.0195

NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; ALI, advanced lung cancer inflammation index; PNI, prognostic nutrition index; ULN, upper limit of normal.

Table S6. Sensitivity analyses of the PFS and OS multivariable Cox regression models.

Outcome	Variable	HR	95% CI	P
PFS	log ₁₀ (IFN-γ + 1)	5.17	2.23–11.99	0.0001
	log ₁₀ (IL-5 + 1)	0.57	0.20–1.62	0.2887
	log ₁₀ (TNF-α + 1)	1.55	0.69–3.50	0.2931
	Liver metastases	3.20	1.73–5.94	0.0002
OS	SIRI	1.11	0.98–1.27	0.1067
	log ₁₀ (IFN-γ + 1)	3.32	1.54–7.16	0.0023
	RDW (>ULN vs. ≤ULN)	2.85	1.23–6.60	0.0142

Cytokines were analyzed after log₁₀(x + 1) transformation; SIRI, systemic inflammation response index; ULN, upper limit of normal.

Table S7. Quantitative assessment of calibration for the PFS and OS prediction models.

Outcome	Time	ICI	E50	E90	Calibration in the large	Optimism-corrected calibration slope
PFS	3 months	0.002	0.003	0.003	-0.002	0.850 (0.358-1.620)
	6 months	0.025	0.028	0.028	-0.009	
	12 months	0.099	0.106	0.111	-0.002	
	12 months	0.044	0.044	0.054	-0.009	0.846 (0.441-1.309)
OS	18 months	0.016	0.010	0.034	-0.004	
	24 months	0.019	0.025	0.033	-0.001	

ICI, E50, and E90 are the mean, median, and 90th percentile of absolute calibration error, respectively. Lower

values indicate better calibration. Calibration slopes were optimism-corrected using 1,000 bootstrap resamples.

Table S8. Dynamic changes in serum cytokine levels from baseline to post-treatment.

Cytokine	Baseline			Post-treatment			<i>P</i>
	Median	Q1	Q3	Median	Q1	Q3	
IFN- α	1.0	0.4	1.9	1.2	0.5	2.5	0.2293
IFN- γ	2.2	1.1	4.4	3.3	2.2	7.0	0.0124
IL-4	1.1	0.9	2.1	1.4	1.0	2.5	0.3651
IL-5	2.3	1.4	3.5	3.2	2.0	4.8	0.0531
IL-17	2.7	1.1	5.6	5.5	2.3	10.7	0.0394
IL-12	1.4	0.8	1.9	1.4	0.8	1.9	0.9955
IL-6	11.1	4.6	28.0	7.8	4.5	25.2	0.8058
IL-8	10.3	0.0	49.2	7.1	0.0	44.4	0.7324
IL-10	1.6	1.1	2.7	2.0	1.3	2.9	0.0772
IL-1 β	2.3	0.6	4.5	2.1	0.5	6.1	0.2300
TNF- α	2.0	0.8	3.4	1.6	0.8	2.6	0.6616

Q1 and Q3 represent the first and third quartiles, respectively.

Table S9. Univariable and multivariable analysis of hematological parameters for predicting immune-related adverse events.

Factor	Univariable			Multivariable		
	OR	95% CI	<i>P</i>	OR	95% CI	<i>P</i>
IL-4						
Low	1			1		
High	2.55	1.06-6.34	0.0396	7.86	2.09-40.5	0.0051
IL-1β						
Low	1			1		
High	2.41	0.91-7.25	0.0919	4.58	1.28-20.70	0.0293
TNF-α						
Low	1			1		
High	0.56	0.23-1.33	0.1872	0.11	0.02-0.47	0.0056
NLR						
Low	1			1		
High	0.42	0.17-1.04	0.0622	0.04	0.01-0.23	0.0013
PLR						
Low	1			1		
High	2.79	1.09-7.82	0.0389	30.4	5.18-330.0	<0.0001

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Table S10. Logistic regression analysis of dynamic changes (Δ) in cytokine levels for predicting the risk of immune-related adverse events.

Cytokine	Univariable		
	OR	95% CI	<i>P</i>
Δ IFN- α	1.06	0.88-1.31	0.5574
Δ IFN- γ	1.01	0.99-1.03	0.4772
Δ IL-4	1.02	0.70-1.48	0.8936
Δ IL-5	1.01	0.96-1.06	0.6856
Δ IL-17	1.01	0.97-1.06	0.6744
Δ IL-12	1.76	0.98-3.66	0.0863
Δ IL-6	1.00	0.99-1.02	0.5744
Δ IL-8	1.00	1.00-1.01	0.4246
Δ IL-10	1.05	0.87-1.30	0.5642
Δ IL-1 β	1.05	1.00-1.14	0.1467
Δ TNF- α	1.48	1.12-2.15	0.0161

The Δ was defined as the post-treatment value minus the baseline value.