

Supplementary Materials

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Supplementary Figures

Figure S1. Cutoff of circulating inflammation biomarkers determined by the Maximally Selected Rank Statistics and survival curves stratified by these cutoffs (a, hyaluronidase [HA]; b, IV collagen [CIV]; c, laminin [LN]; d, procollagen III [PIIIPN.P]; e, neutrophil to lymphocyte ratio [NLR]; f, platelet to lymphocyte ratio [PLR]; g, lymphocyte to monocyte ratio [LMR]; h, high-density lipoprotein [HDL]; i, lactate dehydrogenase [LDH]; j, C-reactive protein [CRP] to albumin ratio [CRP/ALB]).

Figure S2. Cutoff of circulating inflammation signature (CISIG) determined by the Maximally Selected Rank Statistics.

Figure S3. Decision curve analyses of the nomogram at 3- and 5-year in training and validation cohort. (a) at 3-year in the training cohort. (b) at 5-year in the training cohort. (c) at 3-year in the validation cohort. (d) at 5-year in the validation cohort.

Figure S4. Survival curves of disease-free survival by treatment in matched patients with high or low circulating inflammation signature (CISIG) derived from the training (a) and validation cohorts (b).

Table S1. The optimal cutoffs and respective LASSO regression coefficients of selected markers in the training cohort.

Markers	Cutoff	Coefficient	Log-rank P value
HA	66.79	0.263	0.024
LN	26.14	-0.218	0.092
PIIINP	18.3	-0.468	0.002
NLR	1.48	-0.212	0.380
PLR	149.29	-0.347	0.057
LMR	2.5	-0.691	0.004
HDL	1.38	-0.214	0.022
LDH	149.9	0.488	0.003
CRP/ALB	0.01	0.659	<0.001

Abbreviation: HA, hyaluronidase; CIV, IV collagen; LN, laminin; PIIINP, procollagen III; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; HDL, high-density lipoprotein; LDH, lactate dehydrogenase; CRP/ALB, C-reactive protein (CRP) to albumin ratio.

Table S2. Patient characteristics stratified by the CISIG in the training cohort.

Variable	Low CISIG (N=427)	High CISIG (N=265)	P value
Age, median [IQR]	43 [36.5, 51]	47 [40, 54]	0.001
Sex			
Female	138 (32.3)	42 (15.8)	<0.001
Male	289 (67.7)	223 (84.2)	
Smoking			0.004
No	271 (63.5)	139 (52.5)	
Yes	156 (36.5)	126 (47.5)	
BMI, median [IQR]	19.83 [18.69, 21.09]	19.36 [18.47, 20.45]	0.003
Histology			0.640
Type I	2(0.5)	2(0.8)	
Type II	425(99.5)	263(99.2)	
T stage			0.029
T1	23(5.4)	13(4.9)	
T2	34(8.0)	14(5.3)	
T3	255(59.7)	139(52.5)	
T4	115(26.9)	99(37.4)	
N stage			0.187
N0	51(11.9)	30(11.3)	
N1	169(39.6)	87(32.8)	
N2	125(29.3)	97(36.6)	
N3	82(19.2)	51(19.2)	
Clinical Stage			0.002
I	6(1.4)	9(3.4)	
II	35(8.2)	7(2.6)	
III	207(48.5)	116(43.8)	
IV	179(41.9)	133(50.2)	
EBV DNA Level			0.002
0-999	253(59.3)	122(46.0)	
1000-9999	98(23.0)	65(24.5)	
10000-99999	57(13.3)	54(20.4)	
100000-999999	17(4.0)	21(7.9)	
\geq 10000000	2(0.5)	3(1.1)	
Treatment			0.101
RT only	37(8.7)	23(8.7)	
CCRT	198(46.4)	144 (54.3)	
ICT+CCRT	192 (45.0)	98 (37.0)	

Abbreviation: CISIG, circulating inflammation signature; IQR, interquartile range; BMI, body mass index; EBV DNA, Epstein–Barr virus DNA; RT, radiotherapy; CCRT, concurrent chemo-radiotherapy; ICT, induction chemotherapy.

Table S3. Patient characteristics stratified by the CISIG in the validation cohort.

Variable	Low CISIG (N=286)	High CISIG (N=171)	P value
Age, median [IQR]	44 [36, 51]	47 [39.5, 53]	0.004
Sex			0.114
Female	81 (28.3)	37 (21.6)	
Male	205 (71.7)	134 (78.4)	
Smoking			0.001
No	179 (62.6)	79 (46.2)	
Yes	107 (37.4)	92 (53.8)	
BMI, median [IQR]	19.60 [18.60, 21.09]	19.60 [18.47, 21.09]	0.638
Histology			1.000
Type I	2(0.7)	1(0.6)	
Type II	284(99.3)	170(99.4)	
T stage			0.105
T1	15(5.2)	10(5.8)	
T2	20(7.0)	12(7.0)	
T3	183(64.0)	91(53.2)	
T4	68(23.8)	58(33.9)	
N stage			0.084
N0	27(9.4)	16(9.4)	
N1	101(35.3)	52(30.4)	
N2	111(38.8)	58(33.9)	
N3	47(16.4)	45(26.3)	
Clinical Stage			0.005
I	4(1.4)	3(1.8)	
II	14(4.9)	8(4.7)	
III	162(56.6)	69(40.4)	
IV	106(37.1)	91(53.2)	
EBV DNA Level			0.058
0-999	152(53.1)	73(42.7)	
1000-9999	67(23.4)	49(28.7)	
10000-99999	53(18.5)	32(18.7)	
100000-999999	10(3.5)	15(8.8)	
\geq 10000000	4(1.4)	2(1.2)	
Treatment			0.033
RT	21(7.3)	17(9.9)	
CCRT	138 (48.3)	99 (57.9)	
NACT+CCRT	127 (44.4)	55 (32.2)	

Abbreviation: CISIG, circulating inflammation signature; IQR, interquartile range; BMI, body mass index; EBV DNA, Epstein–Barr virus DNA; RT, radiotherapy; CCRT, concurrent chemo-radiotherapy; NACT, neoadjuvant chemotherapy.

Table S4. Patient characteristics stratified by treatment in matched patients derived from the training cohort (limited to stage III & IV patients with RT alone patients excluded).

Variable	CCRT (N=168)	ICT plus CCRT (N=168)	<i>P</i> value
Age			0.582
>45	76 (45.2%)	70 (41.7%)	
≤45	92 (54.8%)	98 (58.3%)	
Sex			1.000
Female	44 (26.2%)	44 (26.2%)	
Male	124 (73.8%)	124 (73.8%)	
Smoking			0.580
No	101 (60.1%)	95 (56.5%)	
Yes	67 (39.9%)	73 (43.5%)	
BMI, mean ± SD	19.8 ± 1.69	19.8 ± 1.69	0.996
Histology	168 (100%)	168 (100%)	1.000.
T stage			0.565
T1	2 (1.19%)	1 (0.60%)	
T2	6 (3.57%)	10 (5.95%)	
T3	121 (72.0%)	112 (66.7%)	
T4	39 (23.2%)	45 (26.8%)	
N stage			0.658
N0	9 (5.36%)	9 (5.36%)	
N1	56 (33.3%)	51 (30.4%)	
N2	61 (36.3%)	72 (42.9%)	
N3	42 (25.0%)	36 (21.4%)	
Clinical Stage			0.826
III	95 (56.5%)	92 (54.8%)	
IV	73 (43.5%)	76 (45.2%)	

Abbreviation: BMI, body mass index; SD, standard deviation; CCRT, concurrent chemo-radiotherapy; ICT, induction chemotherapy.

Table S5. Patient characteristics stratified by treatment in matched patients derived from the validation cohort (limited to stage III & IV patients with RT alone patients excluded).

Variable	CCRT (N=113)	ICT plus CCRT (N=113)	<i>P</i> value
Age			0.894
>45	57 (50.4%)	55 (48.7%)	
≤45	56 (49.6%)	58 (51.3%)	
Sex			0.306
Female	29 (25.7%)	37 (32.7%)	
Male	84 (74.3%)	76 (67.3%)	
Smoking			0.500
No	69 (61.1%)	63 (55.8%)	
Yes	44 (38.9%)	50 (44.2%)	
BMI, mean ± SD	19.8 ± 1.88	20.0 ± 1.65	0.398
Histology			1.000
Type I	0 (0.00%)	1 (0.9%)	
Type II	113 (100%)	112 (99.1%)	
T stage			0.810
T1	4 (3.54%)	4 (3.54%)	
T2	5 (4.42%)	3 (2.65%)	
T3	79 (69.9%)	76 (67.3%)	
T4	25 (22.1%)	30 (26.5%)	
N stage			0.857
N0	8 (7.08%)	6 (5.31%)	
N1	36 (31.9%)	33 (29.2%)	
N2	53 (46.9%)	59 (52.2%)	
N3	16 (14.2%)	15 (13.3%)	
Clinical Stage			0.678
III	74 (65.5%)	70 (61.9%)	
IV	39 (34.5%)	43 (38.1%)	

Abbreviation: BMI, body mass index; SD, standard deviation; CCRT, concurrent chemo-radiotherapy; ICT, induction chemotherapy.

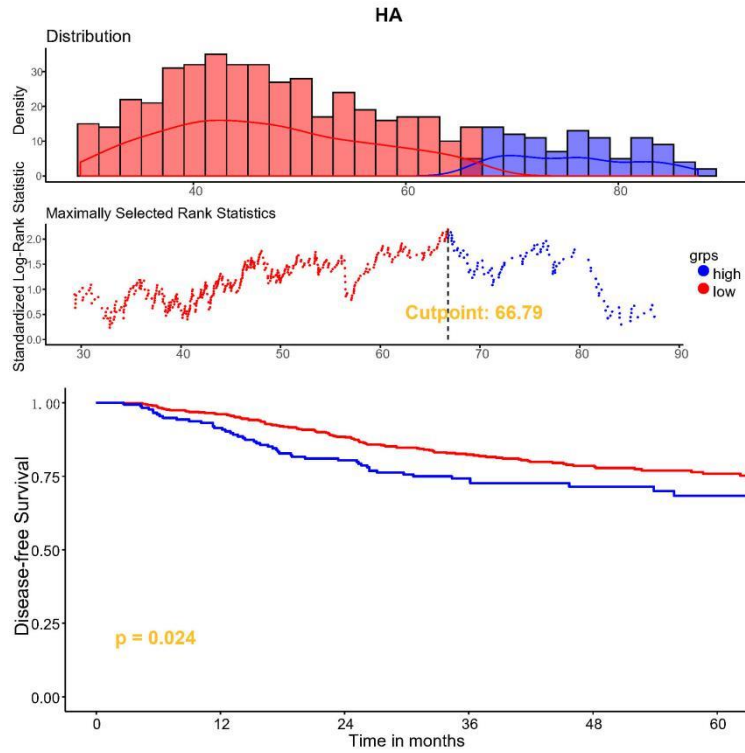


Figure S1a. Cutoff of HA determined by the Maximally Selected Rank Statistics and survival curves stratified by the cutoff.

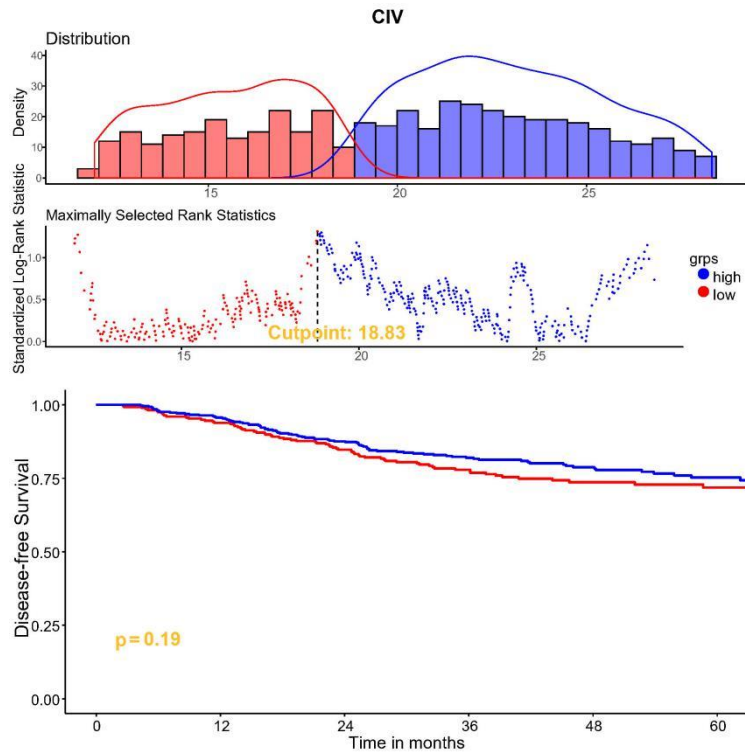


Figure S1b. Cutoff of CIV determined by the Maximally Selected Rank Statistics and survival curves stratified by the cutoff.

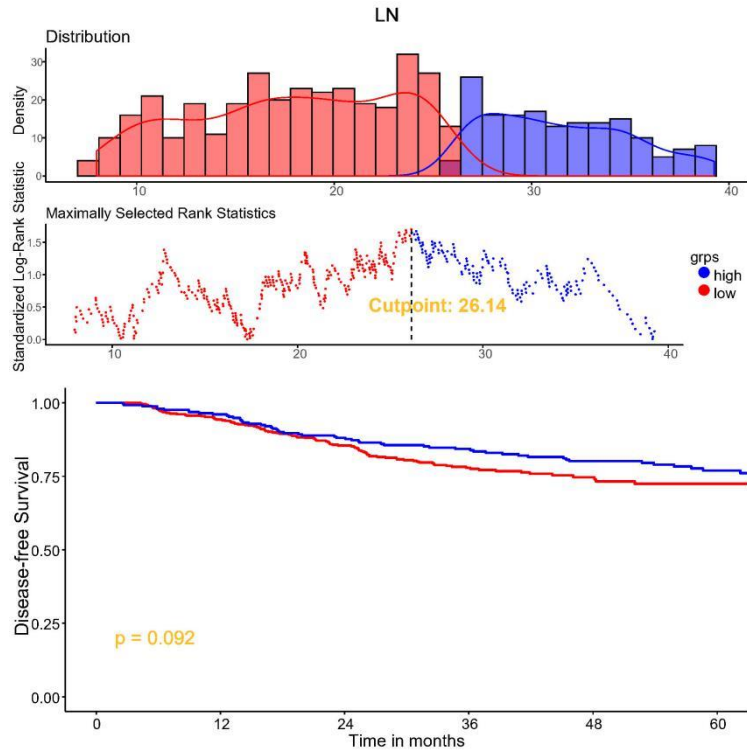


Figure S1C. Cutoff of LN determined by the Maximally Selected Rank Statistics and survival curves stratified by the cutoff.

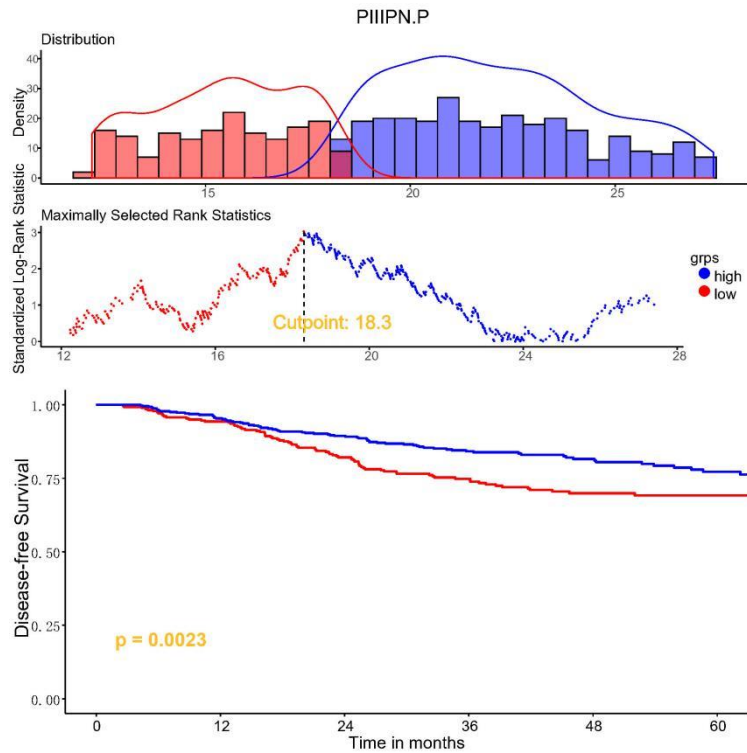


Figure S1D. Cutoff of PIIPN.P determined by the Maximally Selected Rank Statistics and survival curves stratified by the cutoff.

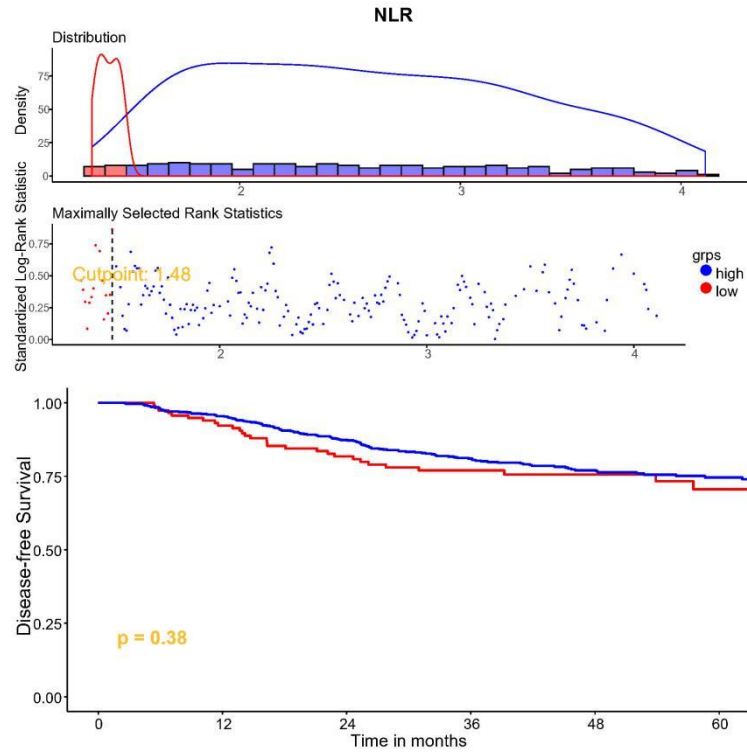


Figure S1e. Cutoff of NLR determined by the Maximally Selected Rank Statistics and survival curves stratified by the cutoff.

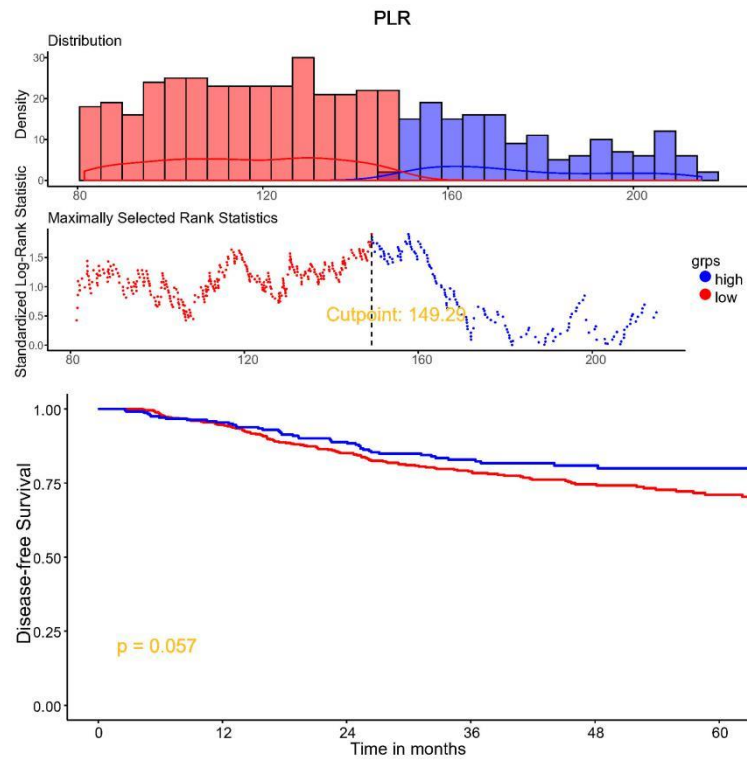


Figure S1f. Cutoff of PLR determined by the Maximally Selected Rank Statistics and survival curves stratified by the cutoff.

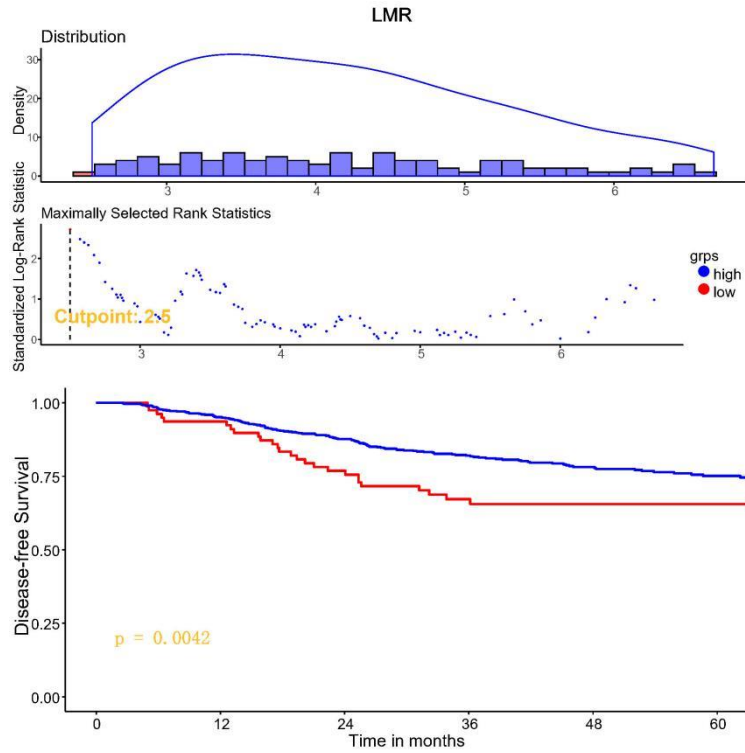


Figure S1g. Cutoff of LMR determined by the Maximally Selected Rank Statistics and survival curves stratified by the cutoff.

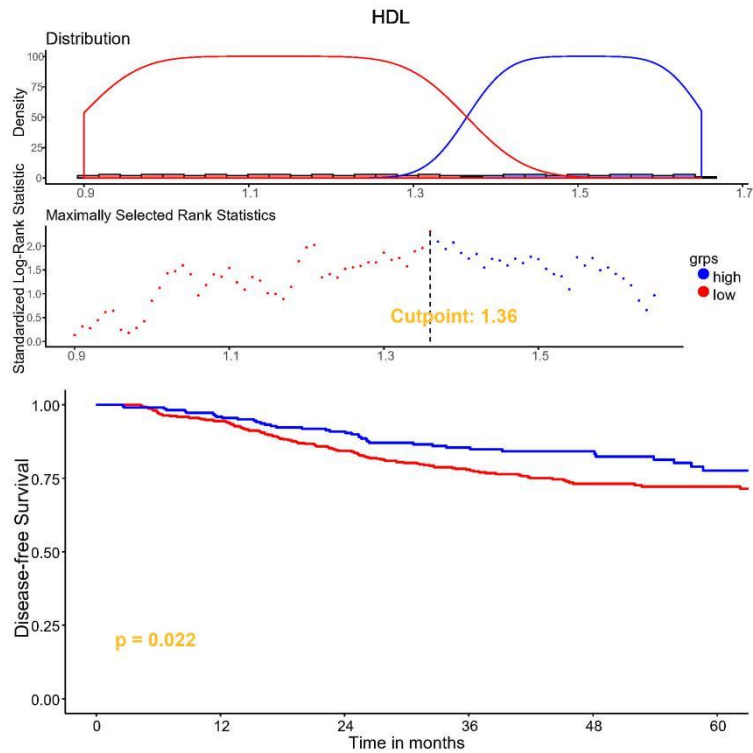


Figure S1h. Cutoff of HDL determined by the Maximally Selected Rank Statistics and survival curves stratified by the cutoff.

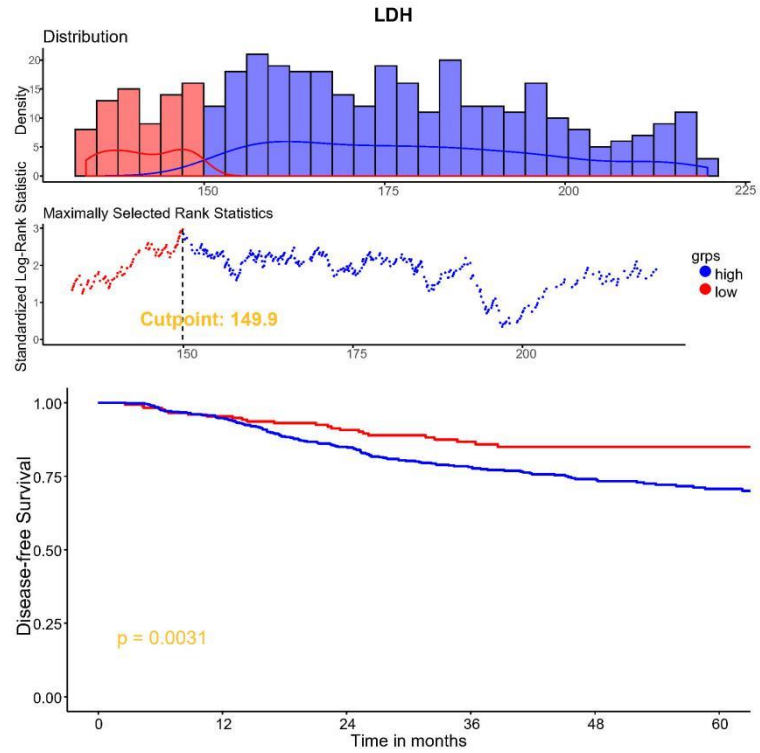


Figure S1i Cutoff of LDH determined by the Maximally Selected Rank Statistics and survival curves stratified by the cutoff.

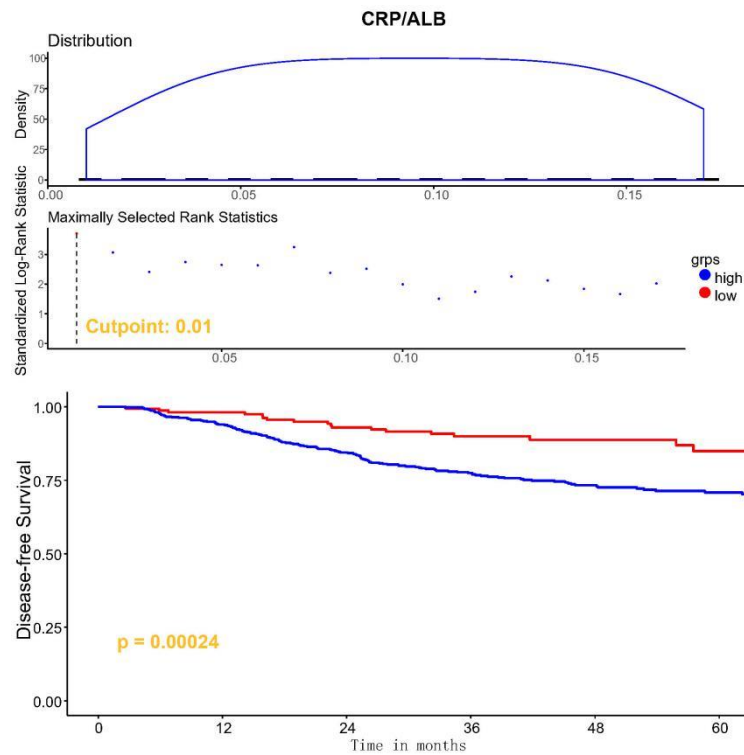


Figure S1j. Cutoff of CRP/ALB determined by the Maximally Selected Rank Statistics and survival curves stratified by the cutoff.

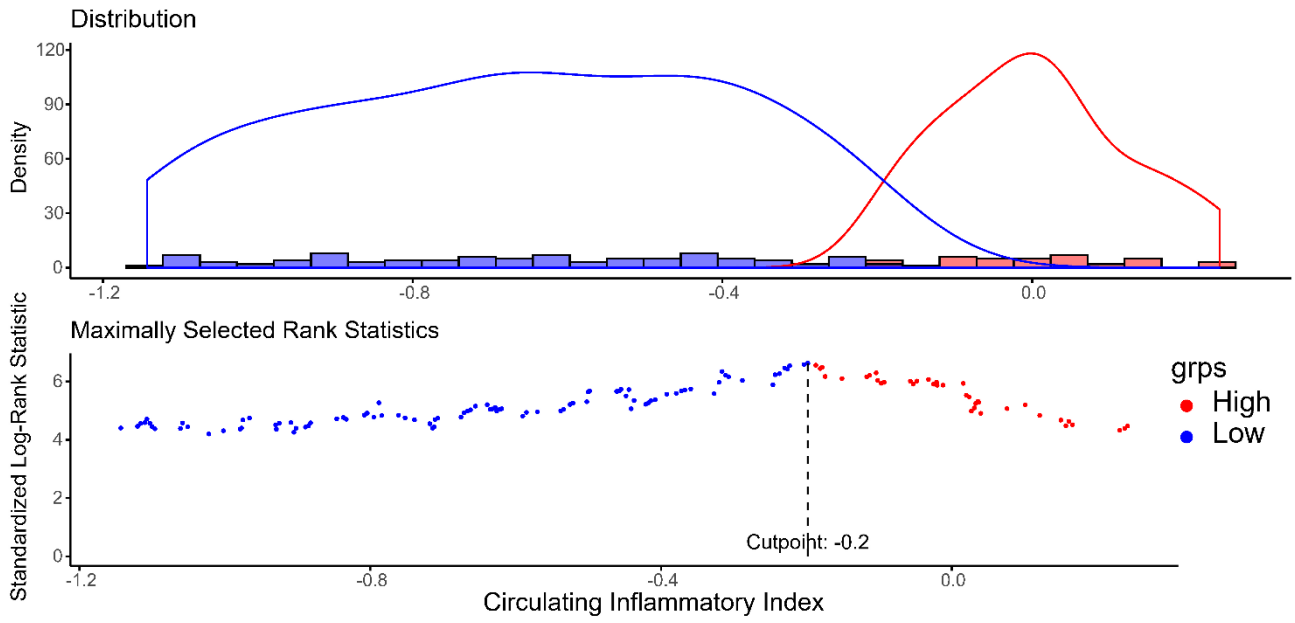


Figure S2. Cutoff of circulating inflammation signature determined by the Maximally Selected Rank Statistics.

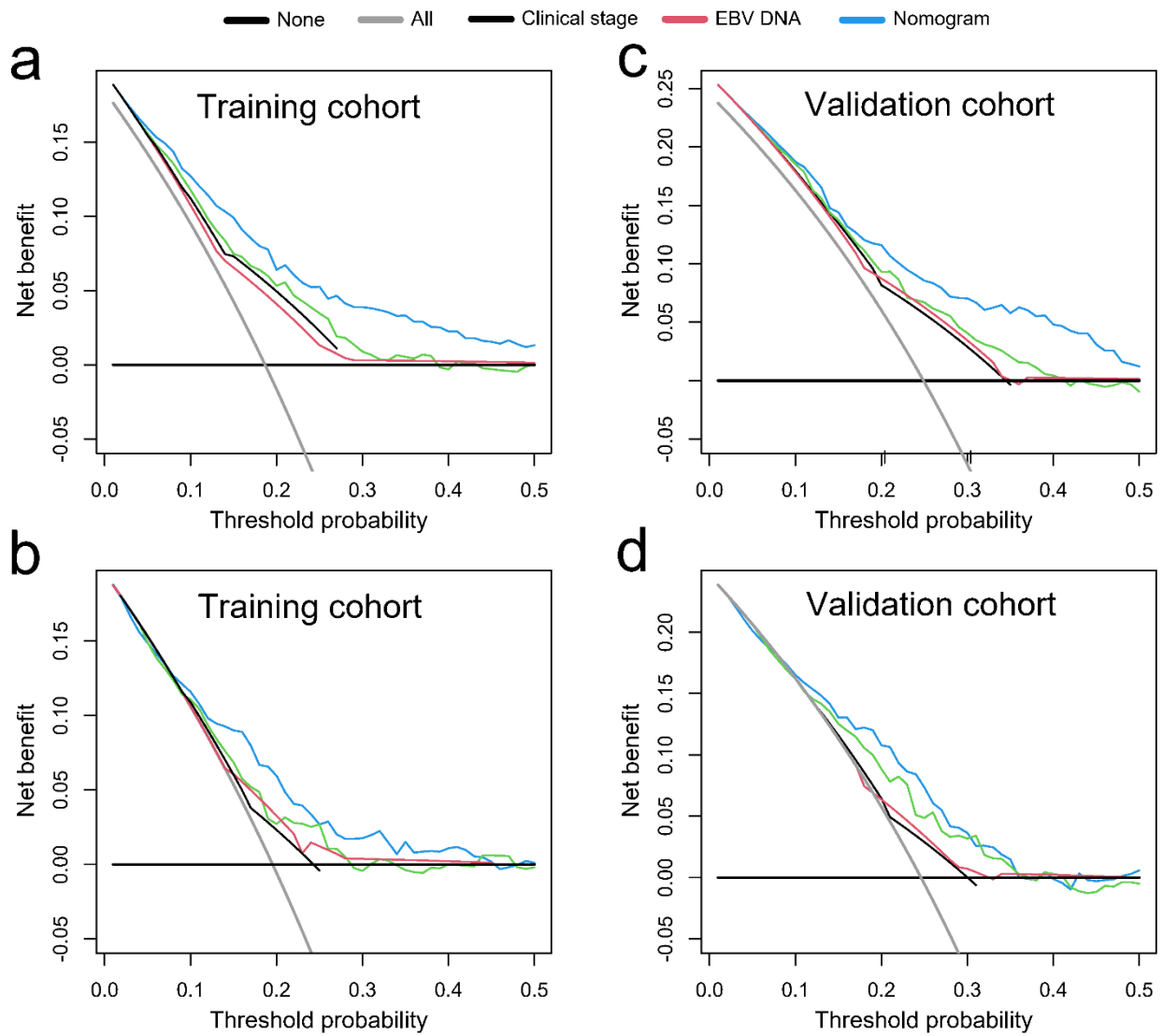


Figure S3. Decision curve analyses of the nomogram at 3- and 5-year in training and validation cohort. (a) at 3-year in the training cohort. (b) at 5-year in the training cohort. (c) at 3-year in the validation cohort. (d) at 5-year in the validation cohort.

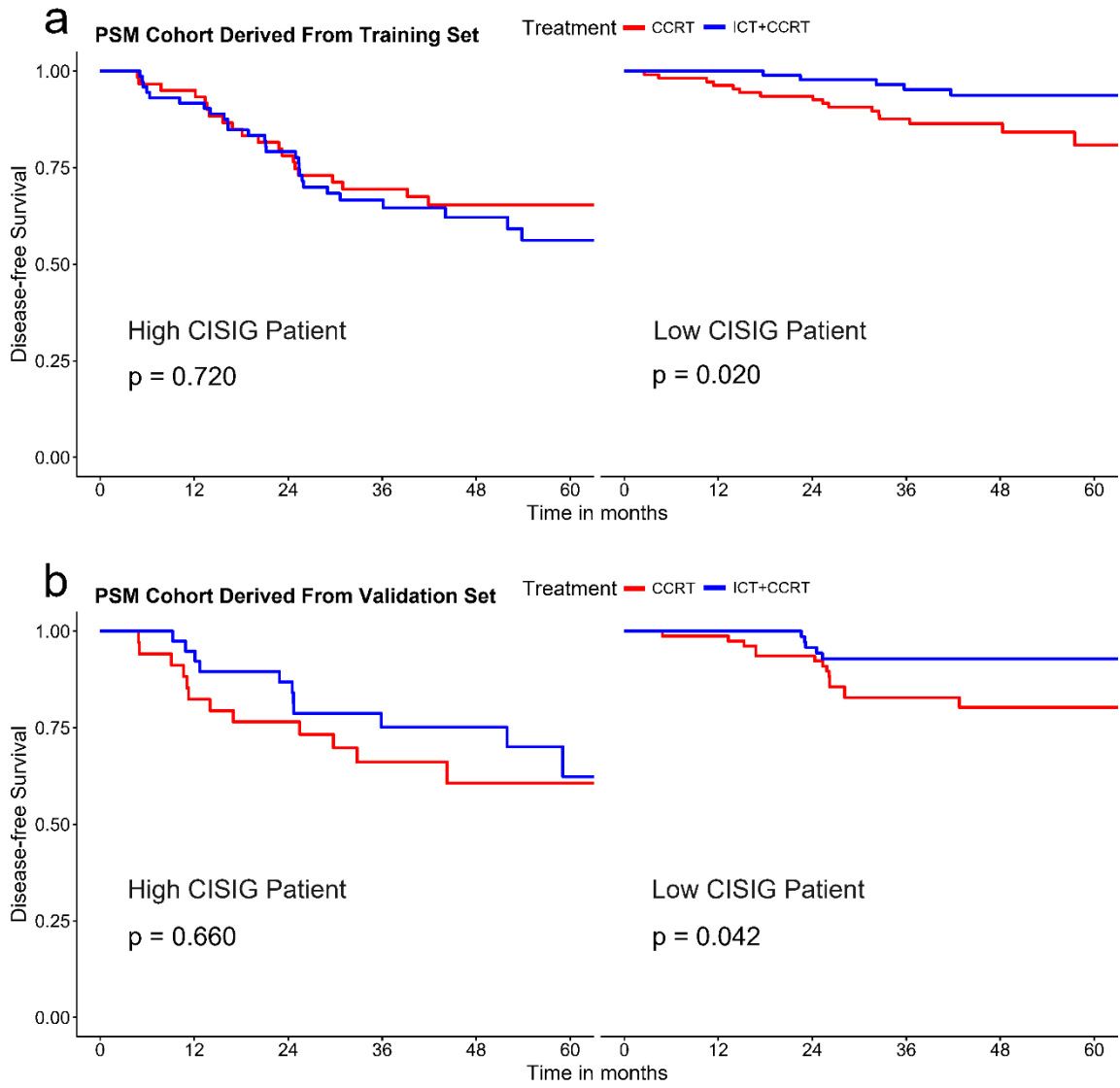


Figure S4. Survival curves of disease-free survival by treatment in matched patients with high or low circulating inflammation signature (CISIG) derived from the training (a) and validation cohorts (b).