

Supplementary Materials

Plasma protein-based signature predicts distant metastasis and induction chemotherapy benefit in nasopharyngeal carcinoma

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Supplementary Methods

Constructing a protein-based signature for metastasis (PSDM) by LASSO cox regression analysis with ten-fold validation

The least absolute shrinkage and selection operator (LASSO) is a popular method for regression with high-dimensional predictors. It introduces a penalty parameter λ to shrink some regression coefficients to exactly zero. The penalty parameter λ , called the tuning parameter, controls the amount of shrinkage: the larger the value of λ , the fewer the number of predictors selected [1]. LASSO has been broadly applied to the Cox proportional hazard regression model for survival analysis to prevent overfitting [2–4]. We selected 17 DMFS-correlated plasma proteins with upregulated tendency and adopted a LASSO Cox regression model to achieve shrinkage and variable selection simultaneously. Ten-fold cross-validation was used to determine the optimal values of λ . In short, the 226 LA-NPC patients were randomly partitioned into 10 equal-sized subsamples. A series of different λ values for LASSO was generated by the “glmnet” package [2] in R software. For each λ , 9 subsamples were used as training data to generate a model, and the remaining 1 subsample was retained to validate the model. The partial likelihood deviance was calculated to evaluate the efficacy variation between the training and validation subsamples. The cross-validation process is then repeated 10 times, with each of the 10 subsamples used exactly once as the validation data. In this way, for each λ , the mean and estimated standard error of the partial likelihood deviances in ten times were calculated. We choose λ via 1-SE (standard error) criteria [3–4], i.e. the optimal λ is the largest value for which the partial likelihood deviance is within one SE of the smallest value of partial likelihood deviance (Figure 1B–C). Based on this λ value, we could obtain the variables whose beta coefficients were not zero, namely SLAMF5 (coefficient = 0.0208), ESM-1 (coefficient = 0.1039), MMP-8 (coefficient = 0.1761), INSR

(coefficient = 0.0161) and Serpin A5 (coefficient = 0.3738). Then we constructed the PSDM with these coefficients, so risk scores = $0.0208 \times$ the concentration of SLAMF5 + $0.1039 \times$ the concentration of ESM-1 + $0.1761 \times$ the concentration of MMP-8 + $0.0161 \times$ the concentration of INSR + $0.3738 \times$ the concentration of Serpin A5.

References:

- (1) Tibshirani R. Regression shrinkage and selection via the LASSO. *J R Statist Soc Series B (Statistical Methodology)*. 1996.
- (2) Tibshirani R. The lasso method for variable selection in the Cox model. *Stat Med* 1997; 16: 385-95
- (3) Zhang JX, Song W, Chen ZH, Wei JH, Liao YJ, Lei J, et al. Prognostic and predictive value of a microRNA signature in stage II colon cancer: a microRNA expression analysis. *Lancet Oncol*. 2013; 14: 1295-306.
- (4) Wei J, Feng Z, Cao Y, Zhao H, Chen Z, Liao B, et al. Predictive value of single-nucleotide polymorphism signature for recurrence in localised renal cell carcinoma: a retrospective analysis and multicentre validation study. *Lancet Oncology*. 2019; 20: 591-600.

Table S1. Clinicopathological characteristics of 16 matched patients with post-treatment metastatic nasopharyngeal carcinoma (MNPC) and post-treatment non-metastatic nasopharyngeal carcinoma (NMNPC).

	MNPC N(%)	NMNPC N(%)	<i>P</i>
Age(Mean±SD)	38.4 ± 13.1	39.1 ± 12.8	
Gender			0.99
Male	6 (75.0)	6 (75.0)	
Female	2 (25.0)	2 (25.0)	
T Stage			0.99
T3	5 (62.5)	5 (62.5)	
T4	3 (37.5)	3 (37.5)	
N Stage			0.99
N1	5 (62.5)	5 (62.5)	
N2	2 (25.0)	2 (25.0)	
N3	1 (12.5)	1 (12.5)	
TNM Stage			0.99
III	4 (50.0)	4 (50.0)	
IV	4 (50.0)	4 (50.0)	
EBV DNA load (copies/mL)			0.99
< 2000	1 (12.5)	2 (25.0)	
≥ 2000	7 (87.5)	6 (75.0)	
Radiotherapy			0.99
3D-CRT or IMRT	8 (100.0)	8 (100.0)	
Chemotherapy			0.99
CCRT ± IC	8 (100.0)	8 (100.0)	

Abbreviations: TNM: tumor-node-metastasis; 3D-CRT: three-dimensional conformal radiotherapy; IMRT: intensity-modulated radiation therapy; CCRT: concomitant chemoradiotherapy; IC: induction chemotherapy.

Table S2. Univariate Cox regression analysis to explore the impact of time interval on clinical outcomes.

	HR	95%CI	P
Distant metastasis-free survival	1.024	(0.992–1.056)	0.148
Disease-free survival	1.016	(0.990–1.042)	0.225
Overall survival	1.011	(0.979–1.043)	0.512

Table S3. The result of differential expression analysis in high-throughput and low-throughput arrays.

Protein	High-throughput array		Low-throughput array	
	log ₂ (Foldchange) (Metastasis/non-metastasis)	<i>P</i>	log ₂ (Foldchange) (Metastasis/non-metastasis)	<i>P</i>
Annexin A5	1.05	0.019	0.83	0.028
BAFF-R	0.82	0.007	0.50	0.054
BID	0.77	0.031	0.97	0.183
CA 15-3†	-0.71	0.030	0.68	0.067
Cadherin-4	1.01	0.010	0.37	0.176
Calsyntenin-1	0.91	0.035	0.22	0.601
CD155†	-4.64	0.014	0.64	0.080
GST-2	0.95	0.045	0.83	0.191
C-IAP2	1.21	0.011	0.44	0.177
CK-18	1.02	0.048	2.02	0.010
CXCL1	1.29	0.033	0.18	0.851
Delta1†	-4.32	0.042	0.29	0.184
DLK-1	0.85	0.025	0.69	< 0.001
EphA2	1.35	0.030	0.36	0.087
ErbB4	1.07	0.040	0.42	0.110
ESM-1	0.70	0.004	0.40	0.029
Ficolin-1	0.77	0.038	0.49	0.038
FLT-3	1.24	0.014	0.71	0.076
GH receptor	0.70	0.038	0.46	0.024
IL-1F10	0.67	0.031	0.26	0.536
IL-27RA	1.12	0.002	0.48	0.010
INSR	0.94	0.014	1.44	< 0.001
PSIP1	0.84	0.031	0.84	0.085
MCP-2	1.09	0.026	0.36	0.023
MMP-8	0.70	0.004	0.65	< 0.001
Neurturin	1.07	0.006	0.32	0.024
NPDC-1	0.60	0.04	0.36	0.015
PDGF-C	0.70	0.013	1.02	0.004
Renin	-1.00	0.047	-0.13	0.515
Semaphorin-4C	1.07	0.045	1.21	0.095
Serpin A5	0.70	0.044	0.29	0.002
Serpin F1	0.69	0.045	0.28	0.086
ShhN	-0.81	0.015	-0.24	0.094
Siglec-9	0.63	0.024	0.37	0.019
SLAMF1	0.99	0.028	0.36	0.029

SLAMF5	0.76	0.013	0.69	< 0.001
SOX2†	0.75	0.009	-0.27	0.676
Thyroglobulin	0.69	0.037	0.87	0.003
TLR4	1.08	0.029	0.46	0.232
TPST-2	1.01	0.027	0.56	0.409
VEGF-A	0.71	0.018	0.51	0.073
VEGF-D	0.64	0.045	0.09	0.644

†The proteins that showed inconsistent trends in high- and low-throughput arrays.

Abbreviations: ShhN: Sonic Hedgehog N-Terminal.

Table S4. Univariate analysis of the 42 differently expressed proteins associated with distant metastasis-free survival.

	DMFS		
	HR	95% CI	P
Annexin A5	1.20	(1.04–1.38)	0.012
BAFF-R	1.23	(1.00–1.50)	0.049
BID	1.04	(0.97–1.11)	0.299
CA 15-3	1.11	(0.97–1.28)	0.115
Cadherin-4	1.20	(0.97–1.49)	0.089
Calsyntenin-1	1.09	(0.89–1.34)	0.414
CD155	1.1	(0.96–1.27)	0.178
SLAMF5	1.46	(1.20–1.78)	<0.001
GST-2	1.06	(0.97–1.17)	0.189
C-IAP2	1.12	(0.94–1.34)	0.202
CK-18	1.11	(1.03–1.19)	0.009
Delta1	1.08	(0.90–1.30)	0.416
ESM-1	1.64	(1.22–2.20)	0.001
EphA2	1.26	(0.99–1.60)	0.058
ErbB4	1.20	(0.95–1.51)	0.127
Ficolin-1	1.31	(1.05–1.62)	0.015
FLT-3	1.16	(1.00–1.35)	0.051
GH receptor	1.30	(0.99–1.70)	0.062
CXCL1	1.01	(0.95–1.07)	0.858
IL-1F10	1.12	(0.89–1.41)	0.334
IL-27RA	1.61	(1.17–2.20)	0.003
INSR	1.33	(1.13–1.57)	0.001
PSIP1	1.11	(0.98–1.25)	0.115
MCP-2	1.35	(0.99–1.85)	0.058
MMP-8	2.11	(1.44–3.09)	<0.001
Neurturin	1.55	(1.06–2.25)	0.022
NPDC-1	1.84	(1.29–2.62)	0.001
PDGF-C	1.26	(1.03–1.53)	0.026
DLK-1	1.44	(1.07–1.95)	0.017
Renin	0.87	(0.64–1.19)	0.393
Semaphorin-4C	1.06	(0.99–1.15)	0.114
Serpin A5	2.80	(1.65–4.76)	<0.001
Serpin F1	1.36	(0.97–1.91)	0.075
ShhN	0.62	(0.39–0.97)	0.037
Siglec-9	1.54	(1.06–2.25)	0.024
SLAMF1	1.32	(1.00–1.75)	0.050
SOX2	0.98	(0.90–1.07)	0.687

Thyroglobulin	1.27	(1.02–1.57)	0.031
TLR4	1.13	(0.97–1.31)	0.123
TPST-2	1.04	(0.95–1.13)	0.405
VEGF-A	1.35	(1.03–1.77)	0.030
VEGF-D	1.07	(0.77–1.48)	0.685

Eight proteins whose concentrations were below LOD were excluded.

Abbreviations: DMFS: distant metastasis-free survival; ShhN: Sonic Hedgehog N-Terminal; LOD: the lower limit of detection.

Table S5. The results of Univariate Cox analysis and differential analysis of the 18 proteins significantly associated with distant metastasis-free survival.

	Univariate analysis for DMFS			Student <i>t</i> -test	
	HR	95% CI	<i>P</i>	log ₂ (FoldChange)	<i>P</i>
Annexin A5	1.20	(1.04–1.38)	0.012	0.83	0.028
BAFF-R*	1.23	(1.00–1.50)	0.049	0.50	0.054
SLAMF5	1.46	(1.20–1.78)	< 0.001	0.69	< 0.001
CK-18	1.11	(1.03–1.19)	0.009	2.02	0.010
ESM-1	1.64	(1.22–2.20)	0.001	0.40	0.029
Ficolin-1	1.31	(1.05–1.62)	0.015	0.49	0.038
IL-27RA	1.61	(1.17–2.20)	0.003	0.48	0.010
INSR	1.33	(1.13–1.57)	0.001	1.44	< 0.001
MMP-8	2.11	(1.44–3.09)	< 0.001	0.65	< 0.001
Neurturin	1.55	(1.06–2.25)	0.022	0.32	0.024
NPDC-1	1.84	(1.29–2.62)	0.001	0.36	0.015
PDGF-C	1.26	(1.03–1.53)	0.026	1.02	0.004
DLK-1	1.44	(1.07–1.95)	0.017	0.69	< 0.001
Serpin A5	2.80	(1.65–4.76)	< 0.001	0.29	0.002
ShhN*	0.62	(0.39–0.97)	0.037	-0.24	0.094
Siglec-9	1.54	(1.06–2.25)	0.024	0.37	0.019
Thyroglobulin	1.27	(1.02–1.57)	0.031	0.87	0.003
VEGF-A*	1.35	(1.03–1.77)	0.030	0.51	0.073

*The 3 proteins that were significantly associated with distant metastasis-free survival in univariate Cox analysis but marginally significant in differential analysis with student *t*-test.

Table S6. Univariate analysis of the 42 differently expressed proteins associated with disease-free survival.

	DFS		
	HR	95% CI	P
Annexin A5	1.20	(1.07–1.34)	0.002
BAFF-R	1.17	(0.99–1.38)	0.058
BID	1.02	(0.97–1.08)	0.431
CA 15-3	0.98	(0.89–1.09)	0.751
Cadherin-4	1.13	(0.95–1.36)	0.166
Calsyntenin-1	1.09	(0.93–1.29)	0.294
CD155	0.98	(0.90–1.07)	0.696
SLAMF5	1.26	(1.04–1.52)	0.017
GST-2	1.08	(1.00–1.16)	0.049
C-IAP2	1.02	(0.90–1.16)	0.780
CK-18	1.08	(1.02–1.15)	0.011
Delta1	1.11	(0.95–1.29)	0.210
ESM-1	1.50	(1.16–1.95)	0.002
EphA2	1.22	(1.01–1.48)	0.043
ErbB4	1.13	(0.94–1.35)	0.184
Ficolin-1	1.27	(1.07–1.52)	0.007
FLT-3	1.12	(0.99–1.27)	0.060
GH receptor	1.16	(0.95–1.41)	0.151
CXCL1	0.99	(0.94–1.03)	0.535
IL-1F10	1.09	(0.91–1.30)	0.365
IL-27RA	1.36	(1.06–1.76)	0.018
INSR	1.13	(1.01–1.27)	0.037
PSIP1	1.09	(0.99–1.19)	0.086
MCP-2	1.12	(0.89–1.41)	0.326
MMP-8	1.54	(1.16–2.03)	0.003
Neurturin	1.41	(1.05–1.91)	0.023
NPDC-1	1.62	(1.19–2.20)	0.002
PDGF-C	1.08	(0.96–1.21)	0.189
DLK-1	1.07	(0.90–1.26)	0.445
Renin	0.85	(0.67–1.09)	0.214
Semaphorin-4C	1.03	(0.97–1.09)	0.309
Serpin A5	1.99	(1.26–3.14)	0.003
Serpin F1	1.13	(0.85–1.50)	0.392
ShhN	0.75	(0.52–1.08)	0.123
Siglec-9	1.14	(0.87–1.49)	0.353
SLAMF1	1.08	(0.85–1.37)	0.510
SOX2	0.98	(0.92–1.05)	0.559

Thyroglobulin	1.14	(0.99–1.32)	0.074
TLR4	1.12	(0.99–1.27)	0.063
TPST-2	1.03	(0.97–1.11)	0.334
VEGF-A	1.16	(0.94–1.42)	0.157
VEGF-D	1.06	(0.82–1.37)	0.645

Eight proteins whose concentration were below LOD were excluded.

Abbreviations: DFS: disease-free survival; ShhN: Sonic Hedgehog N-Terminal. LOD: the lower limit of detection.

Table S7. Univariate analysis of the 42 differently expressed proteins associated with overall survival.

	OS		
	HR	95% CI	P
Annexin A5	1.19	(1.05–1.36)	0.006
BAFF-R	1.11	(0.90–1.35)	0.328
BID	1.00	(0.94–1.07)	0.901
CA 15-3	0.94	(0.83–1.07)	0.336
Cadherin-4	1.06	(0.86–1.32)	0.584
Calsyntenin-1	1.02	(0.83–1.24)	0.866
CD155	0.97	(0.87–1.08)	0.580
SLAMF5	1.31	(1.06–1.63)	0.014
GST-2	1.06	(0.97–1.15)	0.233
C-IAP2	1.01	(0.86–1.18)	0.890
CK-18	1.05	(0.98–1.13)	0.153
Delta1	1.05	(0.88–1.24)	0.599
ESM-1	1.46	(1.09–1.95)	0.011
EphA2	1.16	(0.90–1.48)	0.246
ErbB4	1.07	(0.86–1.33)	0.531
Ficolin-1	1.21	(0.99–1.49)	0.068
FLT-3	1.00	(0.87–1.15)	0.999
GH receptor	1.12	(0.88–1.42)	0.376
CXCL1	1.03	(0.96–1.09)	0.409
IL-1F10	1.00	(0.81–1.24)	0.979
IL-27RA	1.27	(0.92–1.76)	0.149
INSR	1.19	(1.02–1.39)	0.023
PSIP1	1.04	(0.93–1.16)	0.490
MCP-2	1.37	(1.00–1.86)	0.048
MMP-8	1.56	(1.09–2.22)	0.014
Neurturin	1.46	(1.01–2.13)	0.047
NPDC-1	1.47	(1.03–2.11)	0.034
PDGF-C	1.12	(0.96–1.32)	0.153
DLK-1	1.18	(0.92–1.51)	0.195
Renin	0.67	(0.50–0.90)	0.008
Semaphorin-4C	1.01	(0.94–1.08)	0.821
Serpin A5	2.53	(1.45–4.39)	0.001
Serpin F1	1.26	(0.90–1.75)	0.176
ShhN	0.61	(0.39–0.94)	0.027
Siglec-9	1.17	(0.83–1.66)	0.374
SLAMF1	0.97	(0.72–1.31)	0.863
SOX2	0.98	(0.90–1.06)	0.603

Thyroglobulin	1.16	(0.96–1.40)	0.134
TLR4	1.08	(0.93–1.25)	0.315
TPST-2	1.02	(0.94–1.11)	0.584
VEGF-A	1.13	(0.88–1.46)	0.327
VEGF-D	1.10	(0.81–1.50)	0.548

Eight proteins whose concentrations were below LOD were excluded.

Abbreviations: OS: overall survival; ShhN: Sonic Hedgehog N-Terminal. LOD: the lower limit of detection.

Table S8. The concentration of the 5 proteins of PSDM signature in high and low metastatic risk group stratified by the PSDM risk score.

	High-risk group (n = 81)	Low-risk group (n = 145)	
	Concentration (Mean ± SD)	Concentration (Mean ± SD)	<i>P</i>
	(log₂ pg/ml)	(log₂ pg/ml)	
SLAMF5	13.46 ± 1.05	12.30 ± 0.93	<0.001
ESM-1	8.81 ± 0.90	8.30 ± 0.62	<0.001
MMP-8	6.96 ± 0.55	5.62 ± 0.84	<0.001
INSR	12.72 ± 2.12	10.90 ± 2.59	<0.001
Serpin A5	14.14 ± 0.53	13.61 ± 0.20	<0.001

Table S9. Five-year distant metastasis-free survival, disease-free survival and overall survival estimates for different groups.

5-year survival	All patients (n = 226)		Low EBV DNA load subgroup (n = 92)		High EBV DNA load subgroup (n = 134)	
	Low risk (n = 145)	High risk (n = 81)	Low risk (n = 64)	High risk (n = 28)	Low risk (n = 81)	High risk (n = 53)
DMFS (%)	94.4	64.2	95.1	85.7	93.8	52.8
(95% CI)	(90.6–98.2)	(54.5–75.5)	(89.8–100)	(73.7–99.7)	(88.6–99.2)	(40.9–68.1)
DFS (%)	81.9	58.0	82.5	78.6	81.3	47.1
(95% CI)	(75.8–88.4)	(48.2–69.8)	(73.7–92.5)	(64.8–95.3)	(73.2–90.3)	(35.4–62.7)
OS (%)	90.2	74.1	92.1	85.7	88.8	67.9
(95% CI)	(85.5–95.2)	(65.1–84.2)	(85.6–99.0)	(73.7–99.7)	(82.1–96.0)	(56.5–81.7)

Abbreviations: DMFS: distant metastasis-free survival; OS: overall survival; DFS: disease-free survival; CI: confidence interval; EBV DNA: Epstein-Barr virus DNA.

Table S10. The number of events for different groups.

Number of events	All patients (n = 226)		Low EBV DNA load subgroup (n = 92)		High EBV DNA load subgroup (n = 134)	
	Low risk (n = 145)	High risk (n = 81)	Low risk (n = 64)	High risk (n = 28)	Low risk (n = 81)	High risk (n = 53)
	Distant metastasis	11	30	4	4	7
Disease progression	29	36	12	6	17	30
Death	17	25	7	4	10	21

Abbreviations: EBV DNA: Epstein-Barr virus DNA.

Table S11. Clinicopathological characteristics of the 84 patients selected by propensity score matching in TPF IC benefit subgroup analysis.

	CCRT plus TPF-IC N(%)	CCRT alone N(%)	<i>P</i>
Total population	42	42	
Age			0.99
< 45 years	23	24	
≥ 45 years	19	18	
Gender			0.35
Male	38	34	
Female	4	8	
T Stage			0.40
T1–2	10	6	
T3–4	32	36	
N Stage			0.99
N0–1	16	16	
N2–3	26	26	
EBV DNA load (copies/mL)			0.50
< 2000	19	15	
≥ 2000	23	27	
Radiotherapy			0.99
3D-CRT or IMRT	42	42	

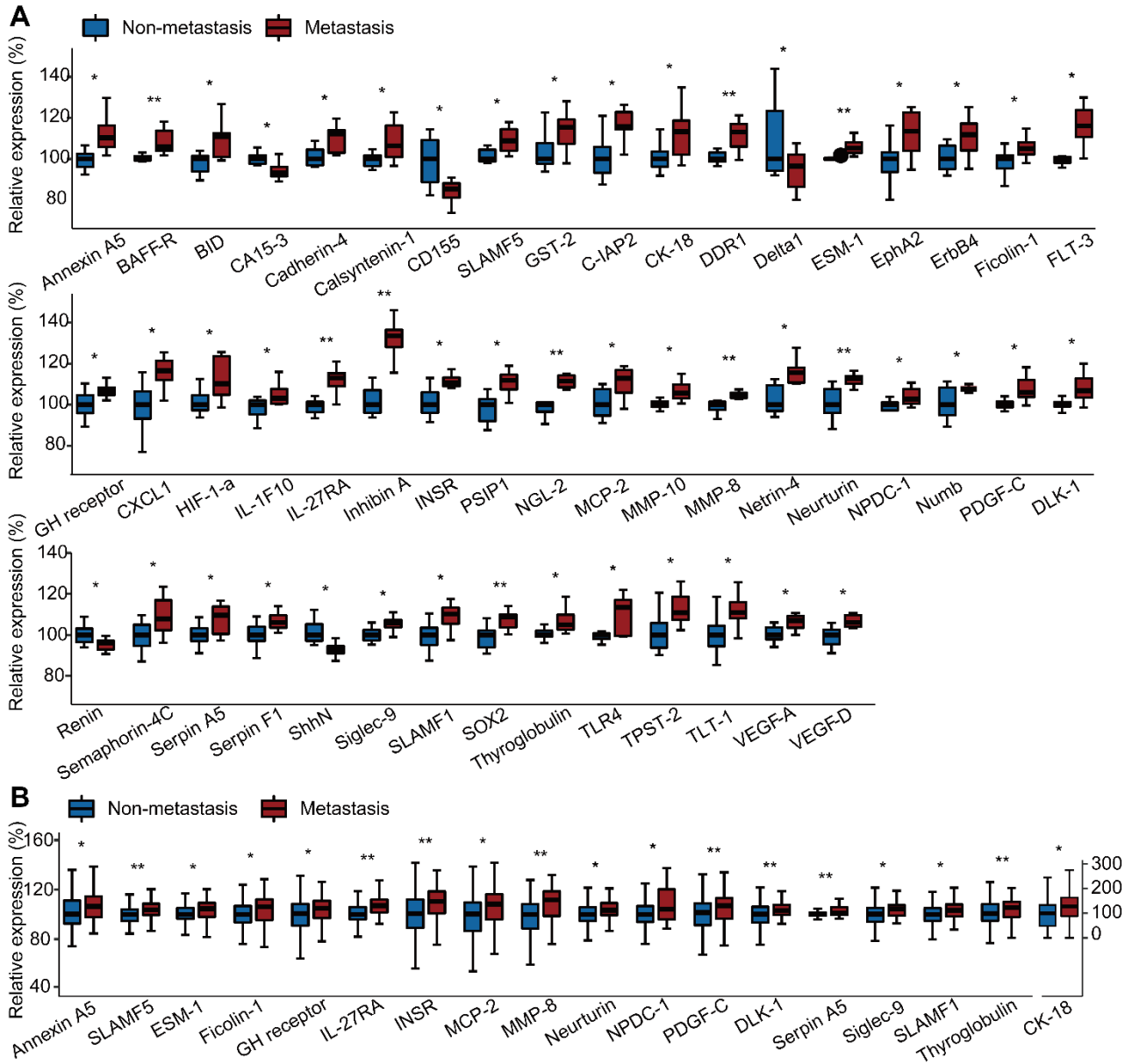


Figure S1. Expression of plasma proteins related to metastasis in the high-throughput and low-throughput arrays.

(A) The 50 differentially expressed proteins discovered using the high-throughput antibody arrays. Student's t-test, * $P < 0.05$, ** $P < 0.01$ (B) The 18 proteins that differentially expressed between metastatic and non-metastatic NPC patients using the low-throughput customized quantitative antibody arrays. Student's t-test, * $P < 0.05$, ** $P < 0.01$. The expression values were log₂-transformed.

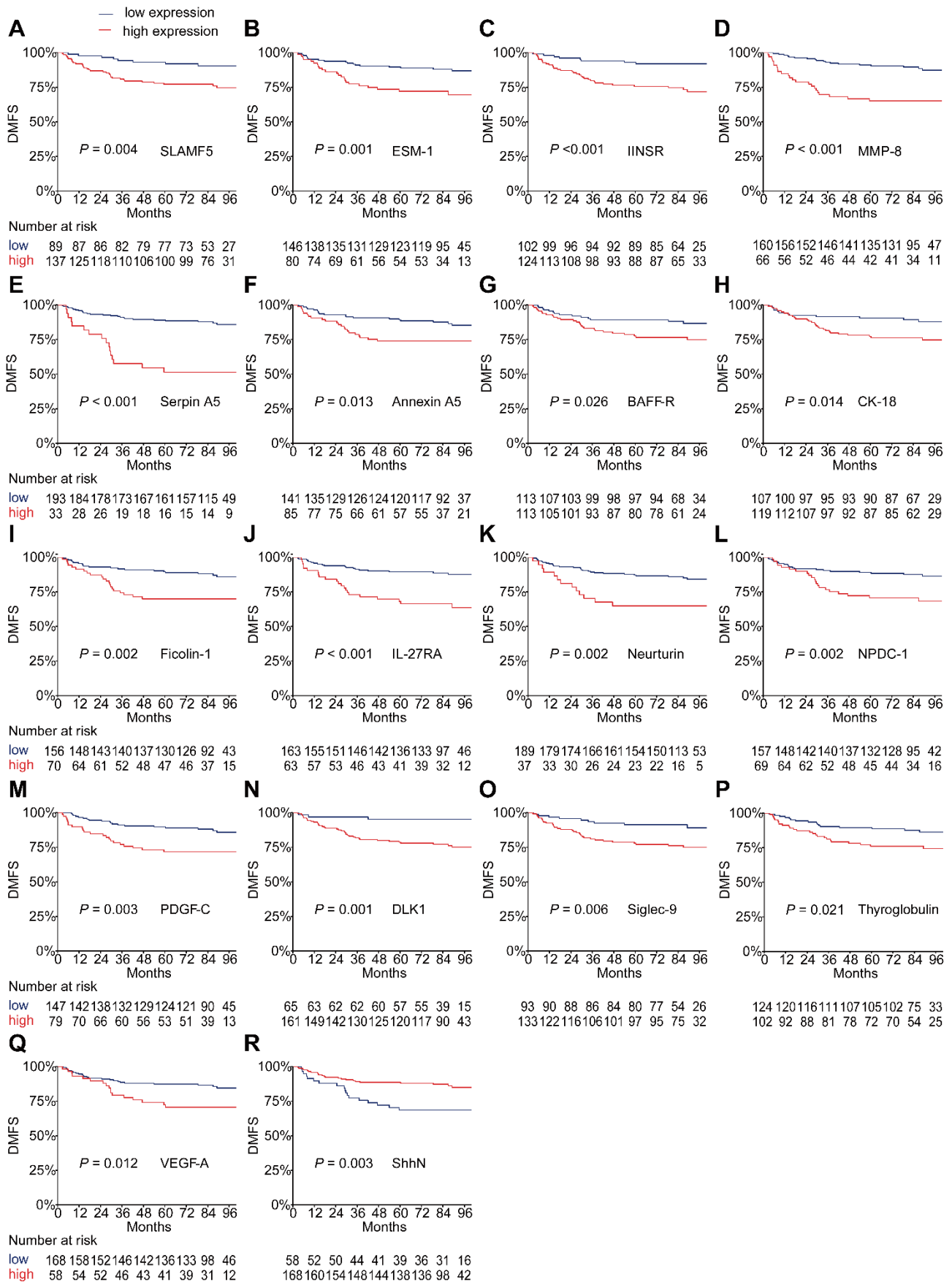


Figure S2. Kaplan–Meier curves of distant metastasis-free survival (DMFS) according to the 18 proteins associated with DMFS.

Plots show (A) SLAMF5; (B) ESM-1; (C) INSR; (D) MMP-8; (E) Serpin A5; (F) Annexin A5; (G) BAFF-R; (H) CK-18; (I) Ficolin-1; (J) IL-27RA; (K) Neurturin; (L) NPDC-1; (M) PDGF-C; (N)DLK1; (O) Siglec-9; (P) Thyroglobulin; (Q) VEGF-A; (R) ShhN.

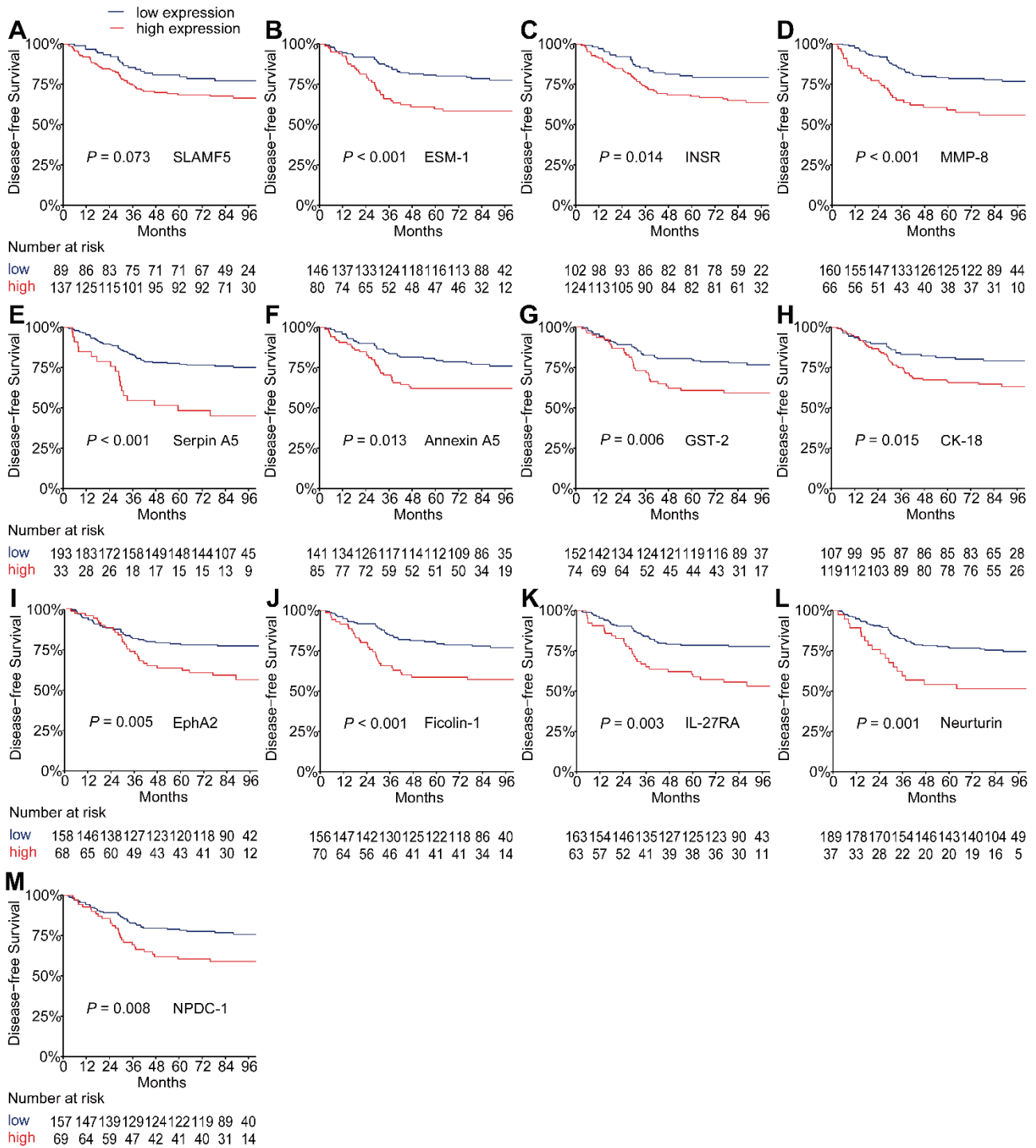


Figure S3. Kaplan–Meier curves of disease-free survival (DFS) according to the 13 proteins associated with DFS.

Plots show (A) SLAMF5; (B) ESM-1; (C) INSR; (D) MMP-8; (E) Serpin A5; (F) Annexin A5; (G) GST-2; (H) CK-18; (I) EphA2; (J) Ficolin-1; (K) IL-27RA; (L) Neurturin; (M) NPDC-1.

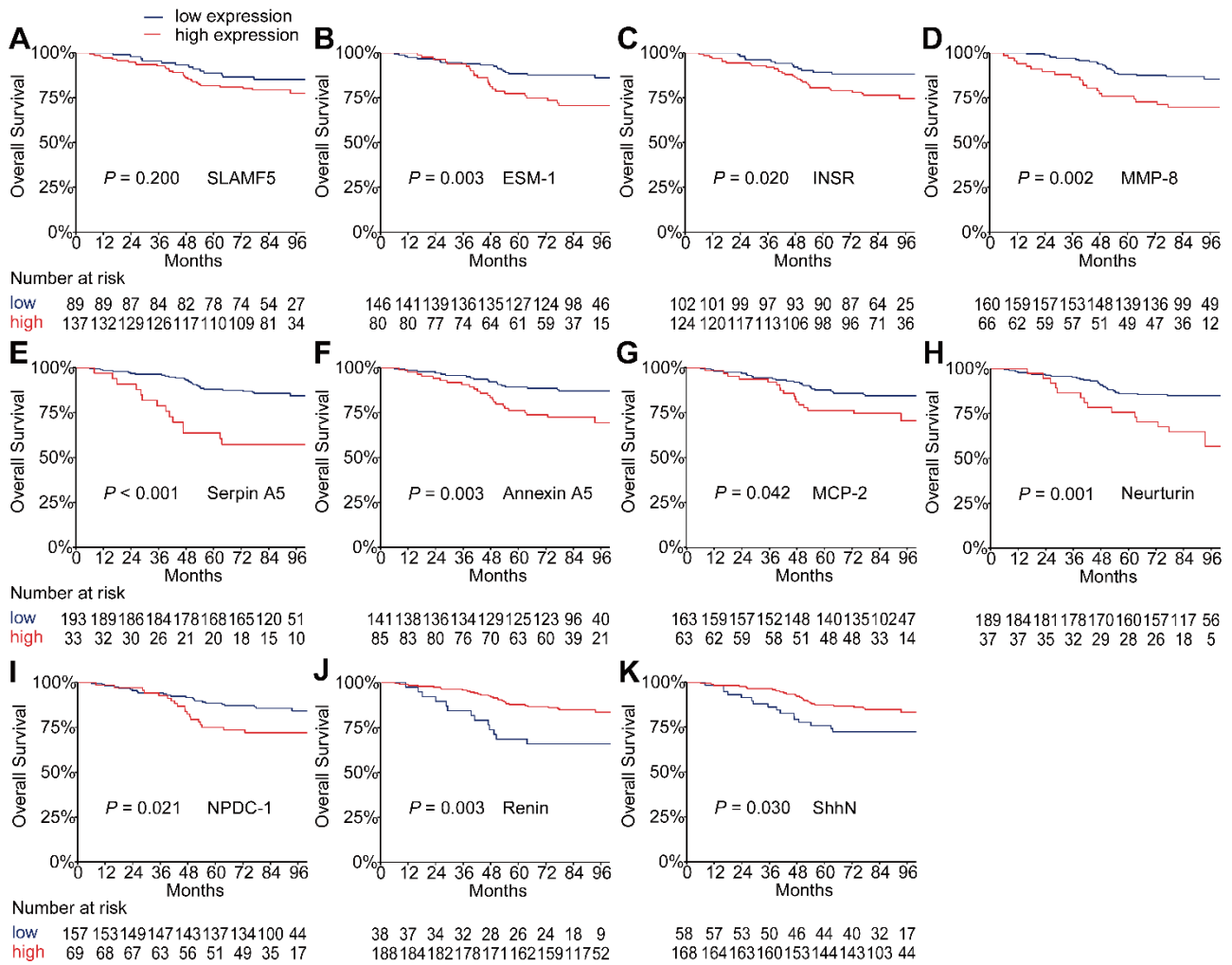
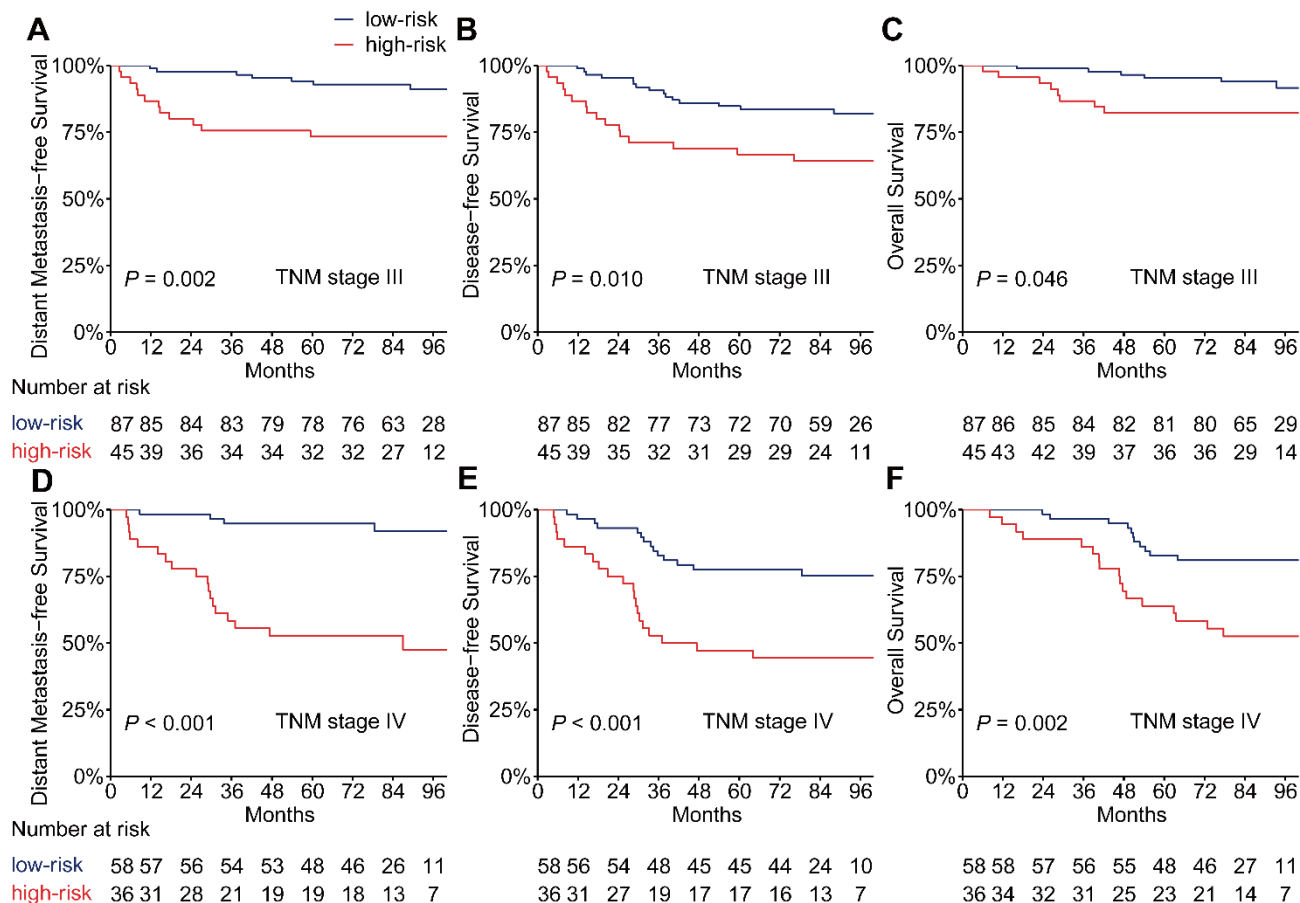
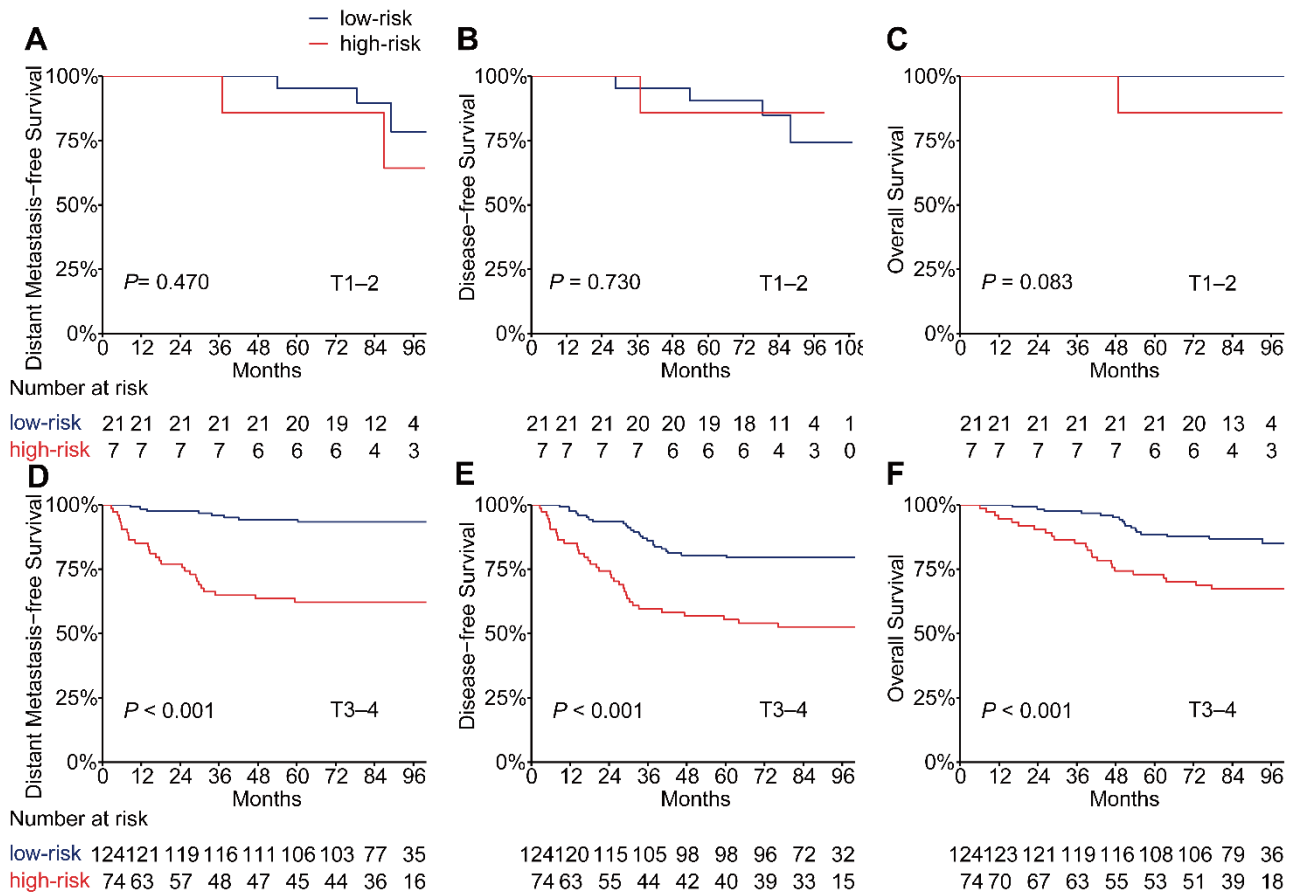
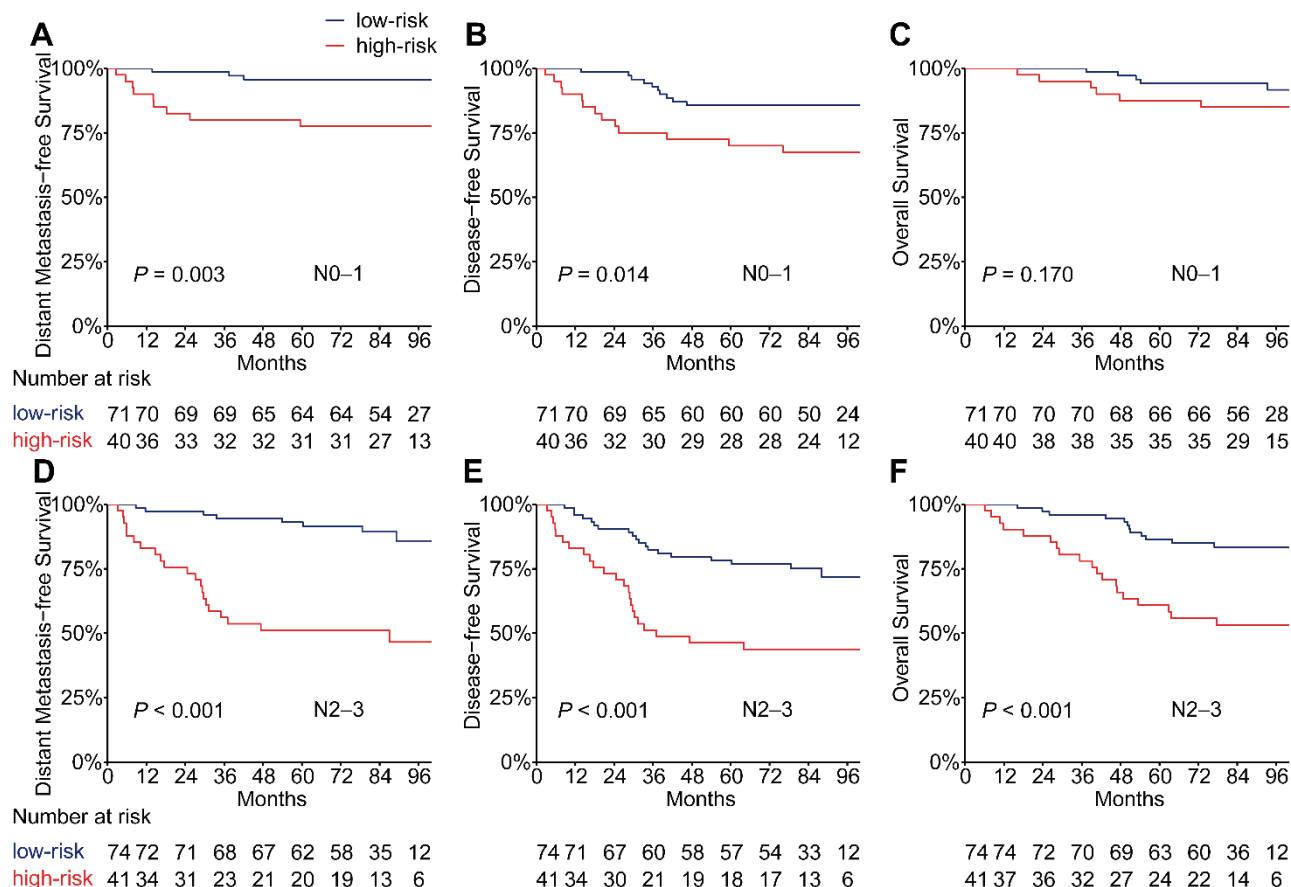


Figure S4. Kaplan–Meier curves of overall survival (OS) according to the 11 proteins associated with OS.

Plots show (A) SLAMF5; (B) ESM-1; (C) INSR; (D) MMP-8; (E) Serpin A5; (F) Annexin A5; (G) MCP-2; (H) Neurturin; (I) NPDC-1; (J) Renin; (K) ShhN.







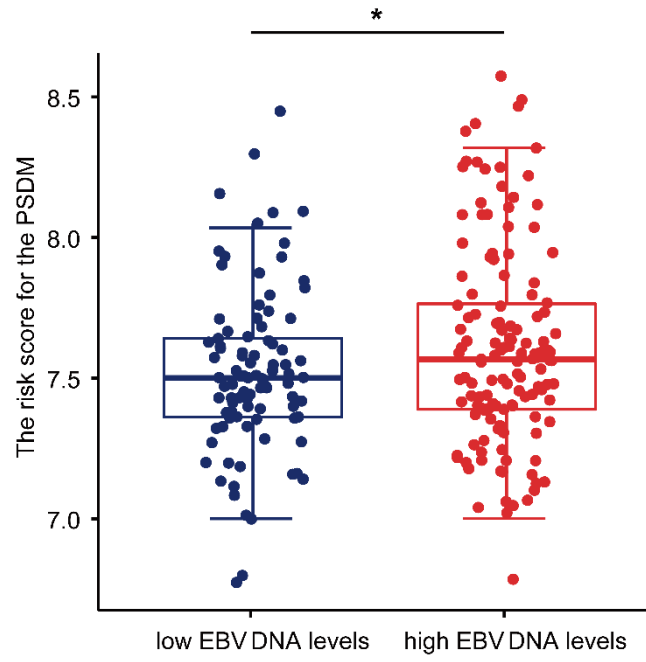


Figure S8. The risk scores for PSDM in the low and high EBV DNA subgroups.