

## Supplementary Material for

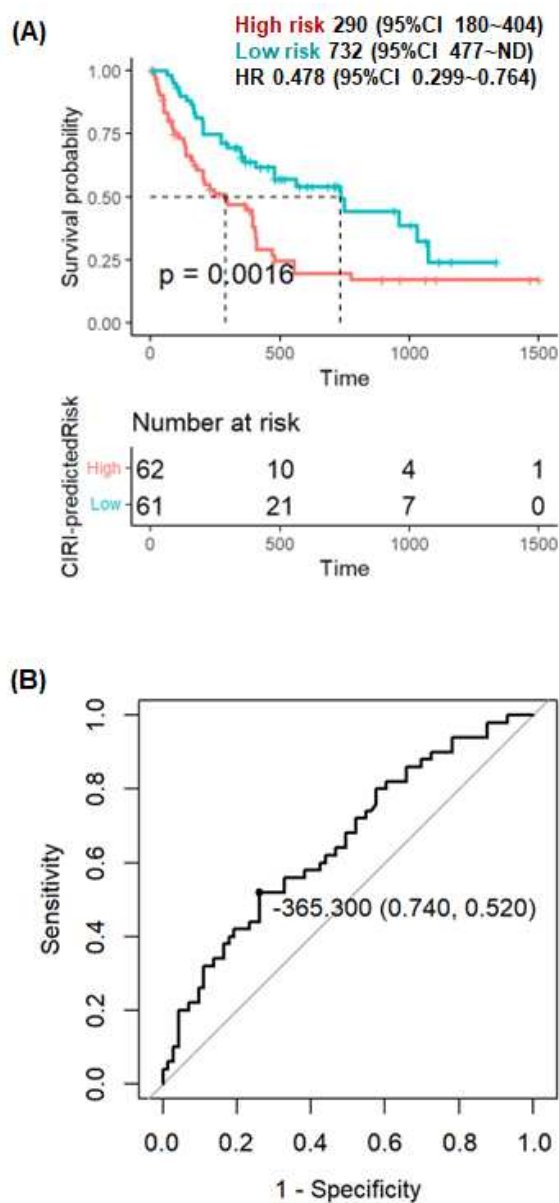
### **Machine Learning for Prediction of Immunotherapeutic Outcome in Non-Small-Cell Lung Cancer based on Circulating Cytokine Signatures**

#### **Contents**

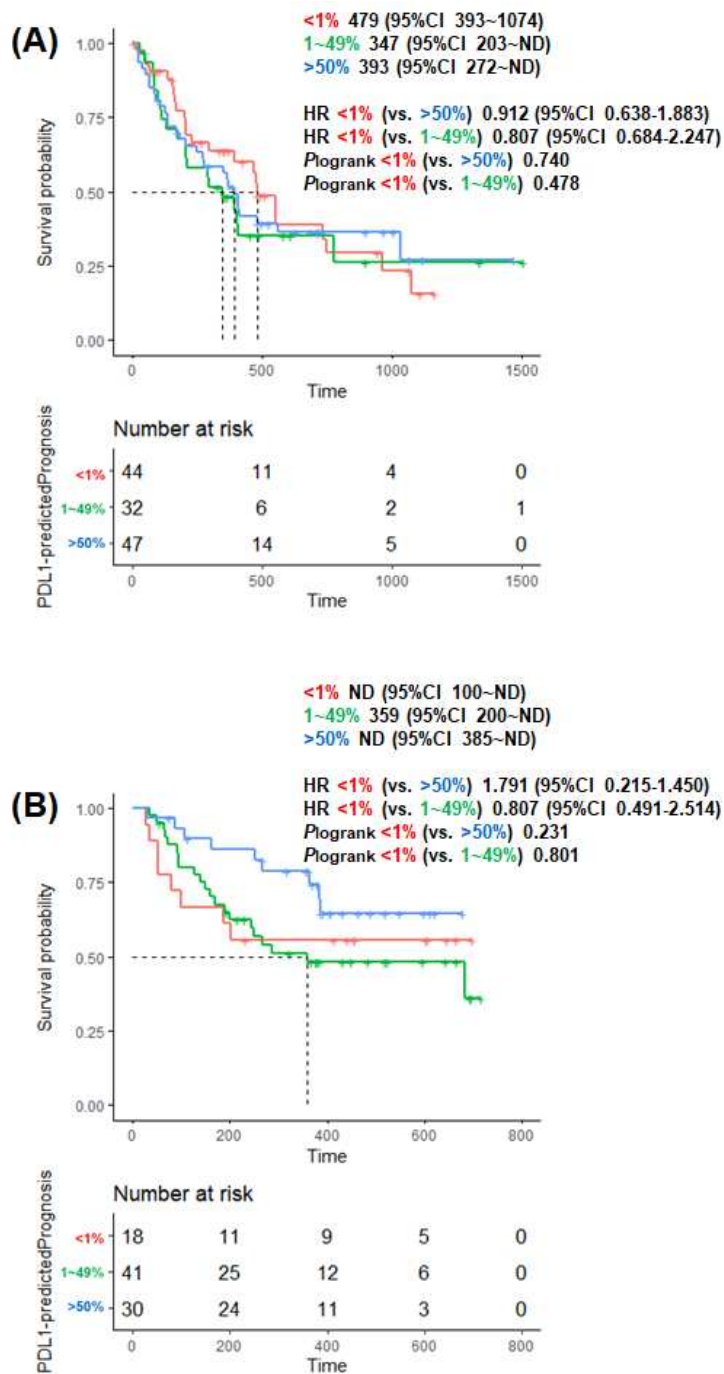
- **Table S1**
- **Figures S1 ~ S8**

**Table S1. Circulating cytokines profiled in the present study**

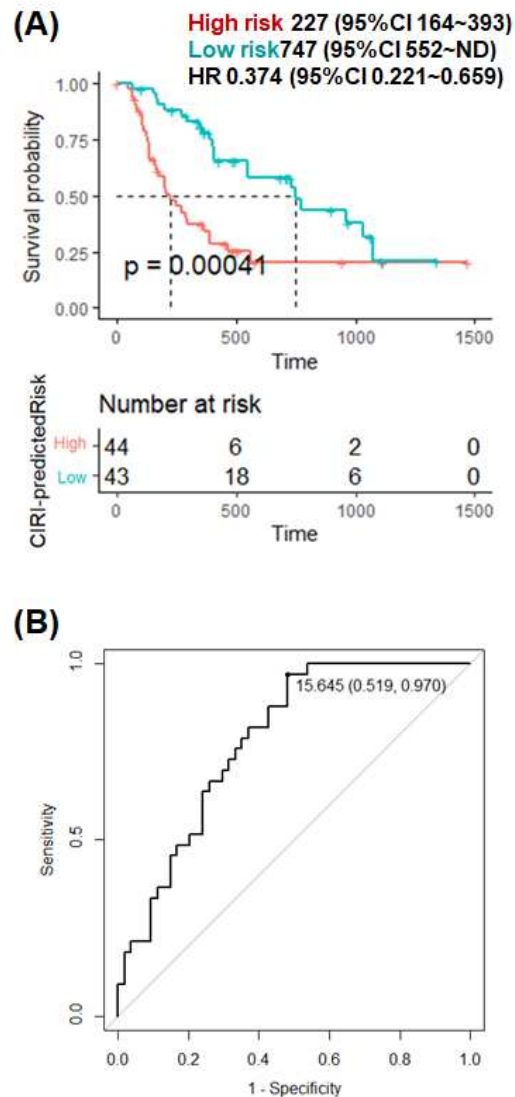
No.	cytokines	No.	cytokines	No.	cytokines
1	APRIL	32	CXCL6	63	IL-33
2	BAFF	33	CXCL9	64	IL-34
3	CCL1	34	FGF-basic	65	IL-35
4	CCL11	35	GM-CSF	66	IL-4
5	CCL13	36	IFN- $\alpha$ 2	67	IL-5
6	CCL15	37	IFN- $\beta$	68	IL-6
7	CCL17	38	IFN- $\gamma$ 2	69	IL-6R $\alpha$
8	CCL19	39	IL-10	70	IL-8
9	CCL2	40	IL-11	71	IL-9
10	CCL20	41	IL-12 (p40)	72	LIGHT
11	CCL21	42	IL-12 (p70)	73	MIF
12	CCL22	43	IL-15	74	MIP-1 $\beta$
13	CCL23	44	IL-16	75	MMP-1
14	CCL24	45	IL-17A	76	MMP-2
15	CCL25	46	IL-17A/F	77	MMP-3
16	CCL26	47	IL-19	78	osteocalcin
17	CCL27	48	IL-1ra	79	osteopontin
18	CCL3	49	IL-1 $\alpha$	80	PDGF-BB
19	CCL5	50	IL-1 $\beta$	81	pentraxin-3
20	CCL7	51	IL-2	82	sCD163
21	CCL8	52	IL-20	83	sCD30
22	chitinase-3-like 1	53	IL-21	84	sCD40L
23	CX3CL1	54	IL-22	85	sIL-6R $\beta$
24	CXCL1	55	IL-23	86	sTNF-R1
25	CXCL10	56	IL-25	87	sTNF-R2
26	CXCL11	57	IL-26	88	TGF- $\beta$ 1
27	CXCL12	58	IL-27	89	TNF $\alpha$
28	CXCL13	59	IL-29	90	TRAIL
29	CXCL16	60	IL-2R $\alpha$	91	TSLP
30	CXCL2	61	IL-31	92	TWEAK
31	CXCL5	62	IL-32	93	VEGF-A



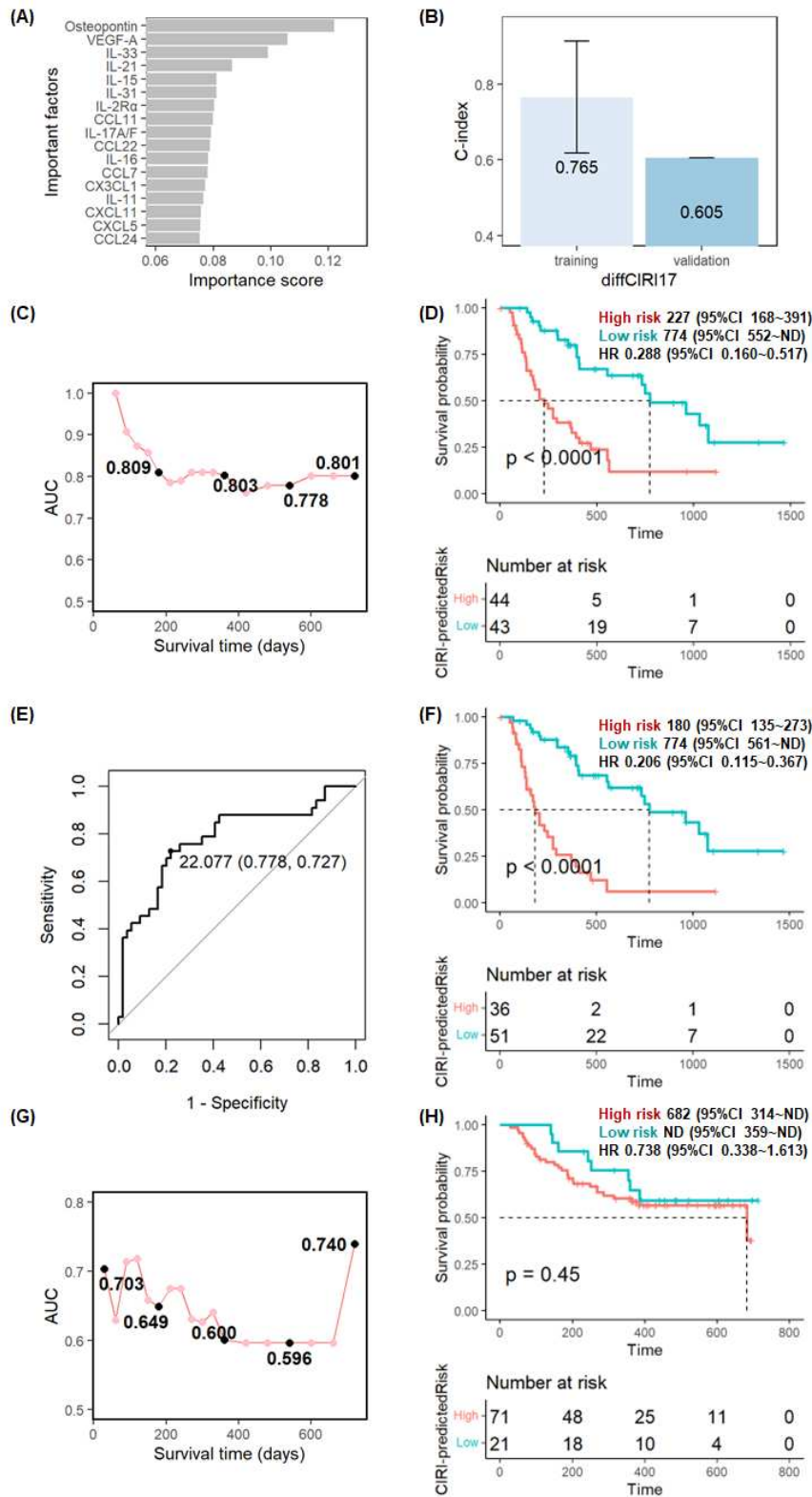
**Figure S1.** (A) Overall survival time of “high risk” and “low risk” groups predicted by preCIRI14 for the training set using cut off value of median; (B) the ROC curve of preCIRI14 at the time point of 1 year after treatment in the training set: the cut off value was optimized using Youden’s  $J$  statistic.



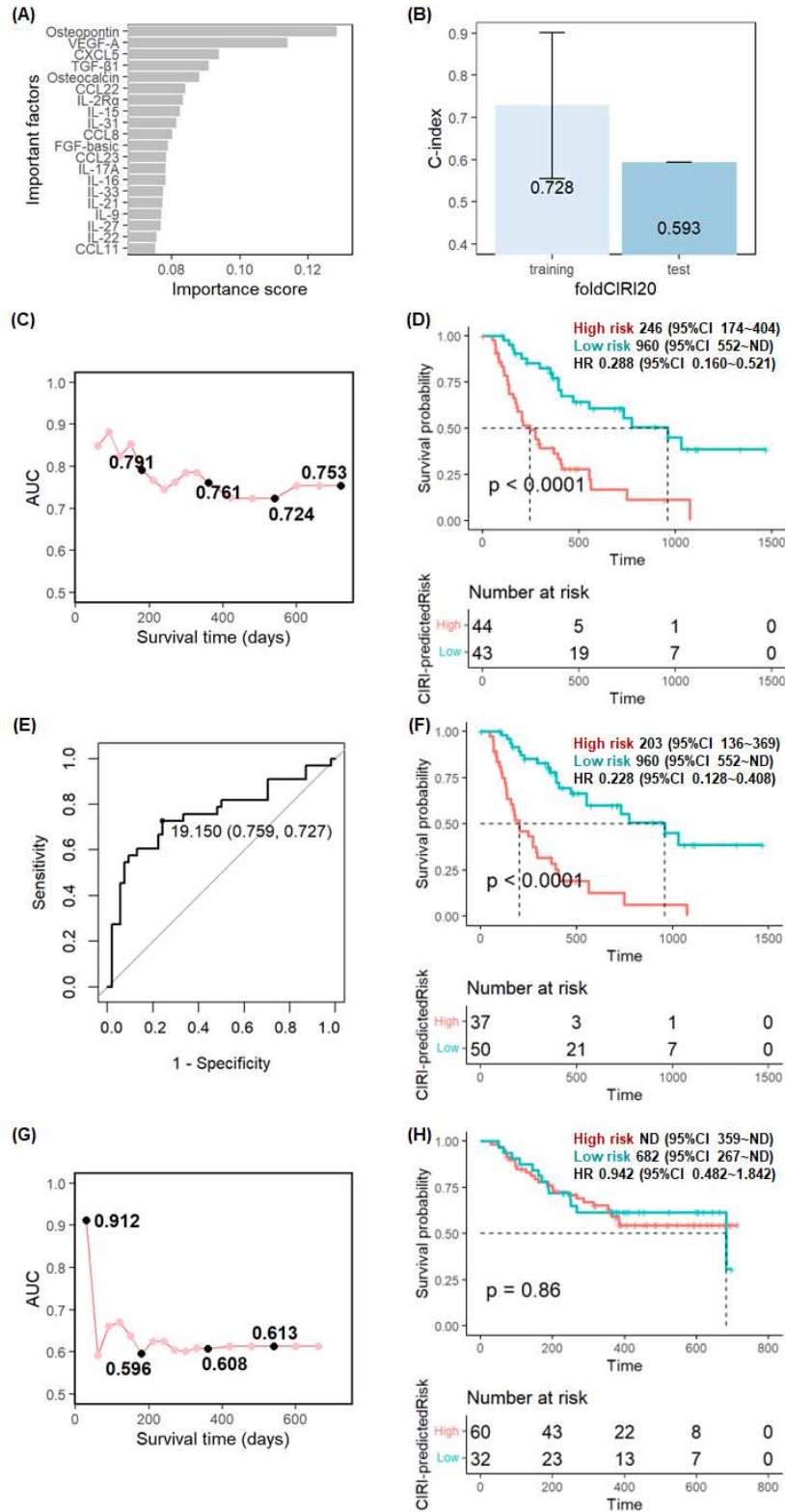
**Figure S2.** Correlation between tumor PD-L1 expression and OS of patients with NSCLC in response to ICI therapy in the **(A)** training and **(B)** validation sets.



**Figure S3.** (A) Overall survival time of “high risk” and “low risk” groups predicted by edtCIRI19 for the training set using cut off value of median; (B) the ROC curve of edtCIRI19 at the time point of 1 year after treatment in the training set: the cut off value was optimized using Youden’s  $J$  statistic.

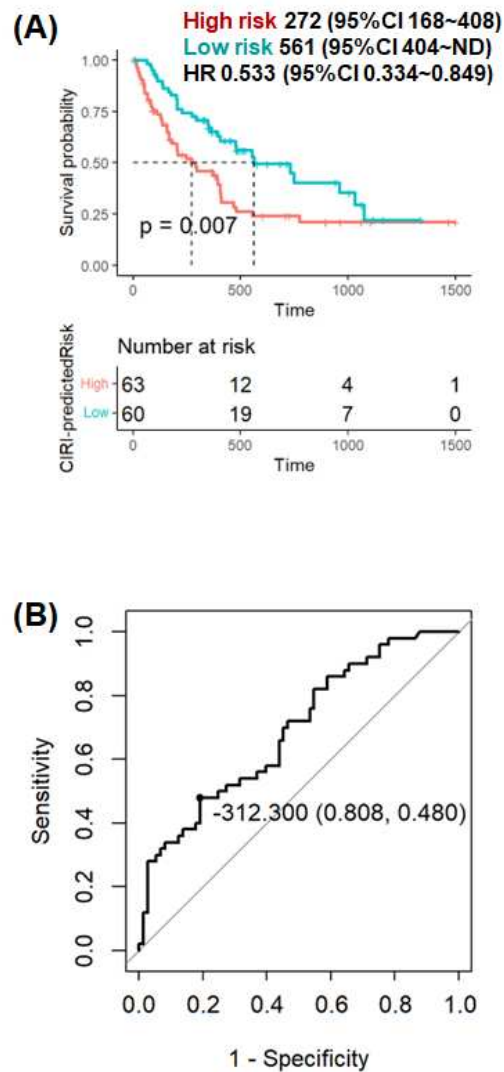


**Figure S4.** Predicting performance of diffCIRI17 model. **(A)** Feature cytokines in change selected using RSF minimal depth filter. The importance score was defined as  $1/(\text{minimal depth})$ ; **(B)** C-indices of diffCIRI17 model for training and validation sets; time-dependent AUC of ROC at each time points for the **(C)** training and **(G)** validation sets; **(D)** overall survival time of “high risk” and “low risk” groups predicted by diffCIRI17 for the training set using cut off value of median; **(E)** the ROC of diffCIRI17 at the time point of 1 year after treatment in the training set: the cut off value was optimized using Youden’s *J* statistic; overall survival time of “high risk” and “low risk” groups predicted by diffCIRI17 for the **(F)** training and **(H)** validation sets using cut off value optimized by the training set. The CIRI scores indicate risk of event occurrence, whereas “high risk” indicates patients with high CIRI scores and “low risk” indicates patients with low CIRI scores.

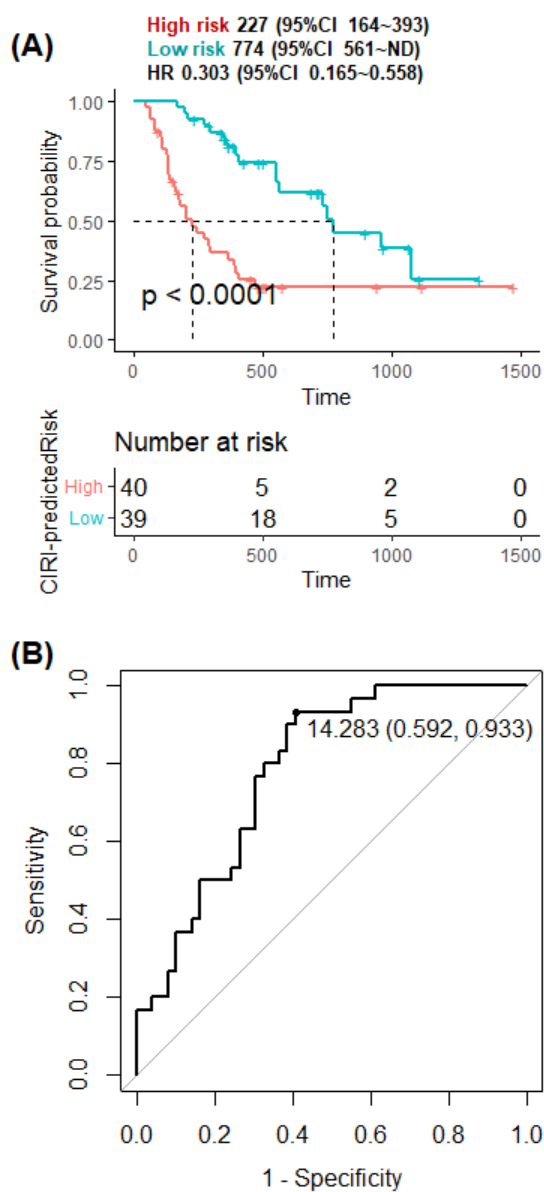




**Figure S5.** Predicting performance of foldCIRI20 model. **(A)** Feature cytokines in change selected using RSF minimal depth filter. The importance score was defined as  $1/(\text{minimal depth})$ ; **(B)** C-indices of foldCIRI20 model for the training and validation sets; time-dependent AUC of ROC at each time points for the **(C)** training and **(G)** validation sets; **(D)** overall survival time of “high risk” and “low risk” groups predicted by foldCIRI20 for the training set using cut off value of median; **(E)** the ROC curve of foldCIRI20 at the time point of 1 year after treatment in the training set: the cut off value was optimized using Youden’s *J* statistic; overall survival time of “high risk” and “low risk” groups predicted by foldCIRI20 for the **(F)** training and **(H)** validation sets using cut off value optimized by training set. The CIRI scores indicate risk of event occurrence, whereas “high risk” indicates patients with high CIRI scores and “low risk” indicates patients with low CIRI scores.

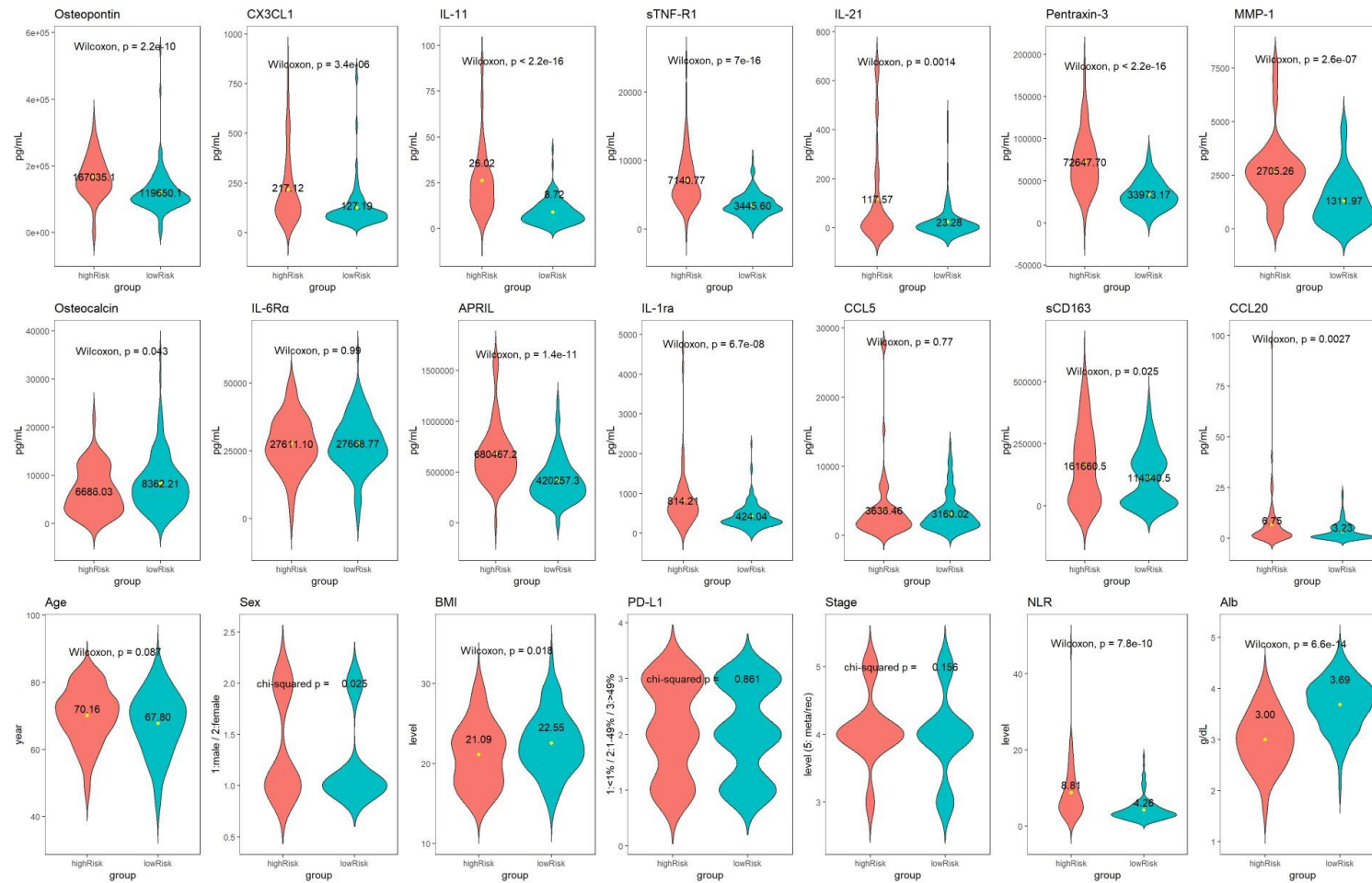


**Figure S6.** (A) Overall survival time of “high risk” and “low risk” groups predicted by preCIRI21 for the training set using cut off value of median; (B) the ROC of preCIRI21 at the time point of 1 year after treatment in the training set: the cut off value was optimized using Youden’s  $J$  statistic.



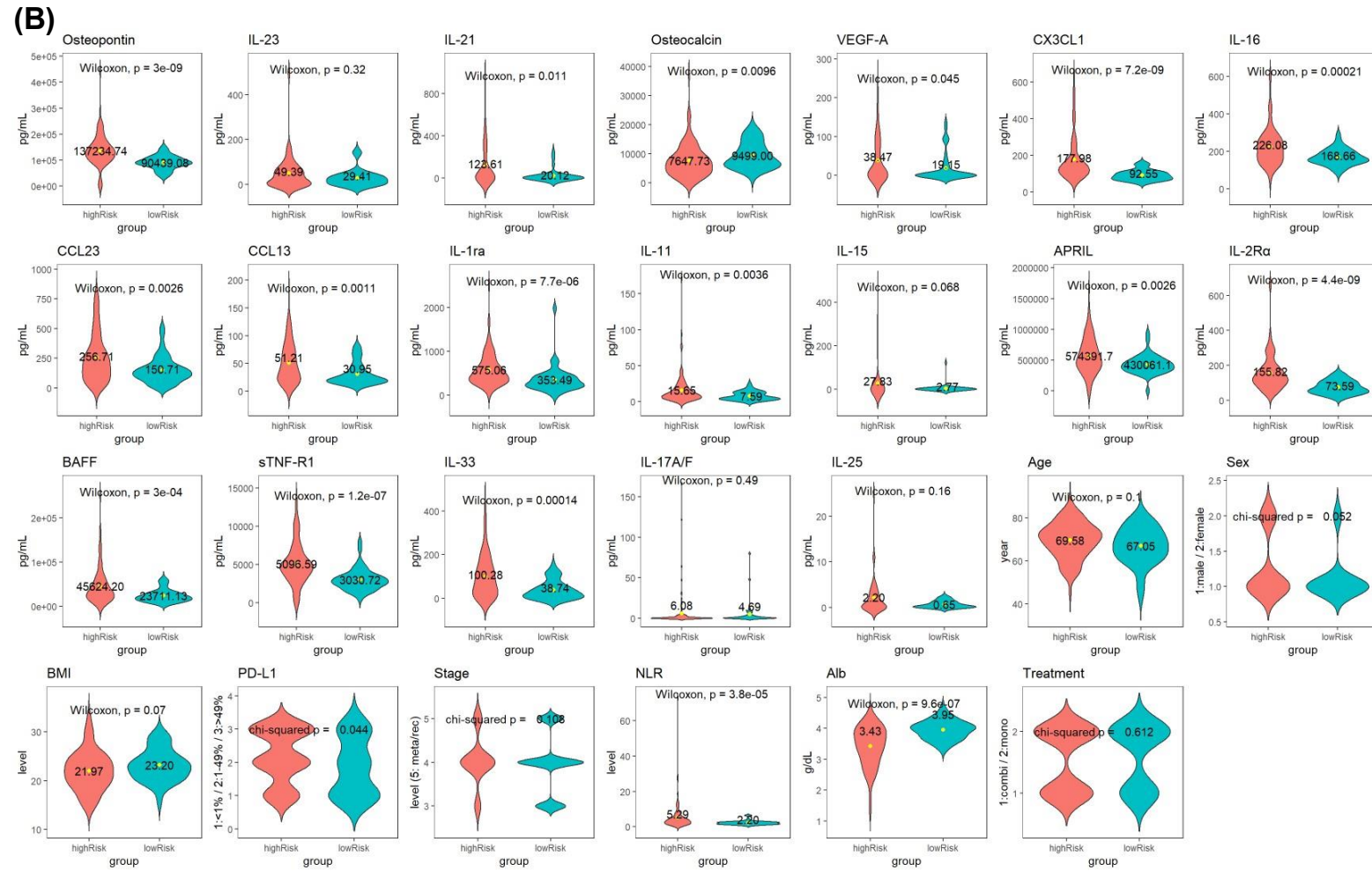
**Figure S7.** (A) Overall survival time of “high risk” and “low risk” groups predicted by edtCIRI27 for the training set using cut off value of median; (B) the ROC of edtCIRI27 at the time point of 1 year after treatment in the training set: the cut off value was optimized using Youden’s  $J$  statistic.

(A)



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1 **Figure S8.** Distribution of the selected feature cytokines and clinical factors in **(A)** preCIRI21 and **(B)** edtCIRI27 of the combined Cohorts  
2 1 and 2. The cut off value of high-/low-risk groups was optimized using Youden's *J* statistic of ROC at the time point of 1 year after  
3 treatment in the training set, as described in **Figures S6** (high risk: preCIRI21  $\geq$  -312.300; low risk: preCIRI21  $<$  -312.300) and **S7** (high  
4 risk: edtCIRI27  $\geq$  14.283; low risk: edtCIRI27  $<$  14.283). Yellow dots indicate the group's mean value for continuous variables.

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