

**Table S1.** Patients' clinical and pathological characteristics.

	Training cohort	Validation cohort	
	MDA	CIBERES <sup>2</sup>	CUN <sup>3</sup>
	MDA <sup>1</sup> n=239	n=75	n=39
<b>Stage</b>			
IA	73 (30.5%)	20 (26.7%)	13 (33.4%)
IA1	4 (1.7%)	2 (2.7%)	4 (10.3%)
IA2	46 (19.2%)	8 (10.7%)	6 (15.4%)
IA3	23 (9.6%)	10 (13.3%)	2 (5.1%)
IB	59 (24.7%)	18 (24.0%)	6 (15.4%)
IIA	14 (5.9%)	4 (5.3%)	2 (5.1%)
IIB	41 (17.2%)	25 (33.3%)	11 (28.2%)
IIIA	39 (16.3%)	8 (10.7%)	7 (17.9%)
IIIB	6 (2.5%)	0 (0%)	0 (0%)
IVA	7 (2.9%)	0 (0%)	0 (0.0%)
<b>Gender</b>			
Male	99 (41.4%)	54 (71.1%)	33 (84.6%)
Female	140 (58.6%)	22 (28.9%)	6 (15.4%)
<b>Age (years)</b>			
<65	33 (13.8%)	42 (55.3%)	24 (61.5%)
≥65	206 (86.2%)	34 (44.7%)	15 (38.5%)
<b>Adjuvant treatment</b>			
No	137 (57.3%)		22 (56.4%)
Yes	87 (36.4%)		17 (43.6%)
Unknown	9 (6.3%)	76 (100%)	0 (0.0%)
<b>Tobacco</b>			
Never	42 (17.6%)		5 (12.8%)
Former	110 (46.0%)		30 (76.9%)
Current	87 (36.4%)		4 (10.3%)
Unknown	0 (0.0%)	76 (100%)	0 (0.0%)

Data are n (%). <sup>1</sup>MDA = M.D. Anderson Cancer Center cohort; <sup>2</sup>CIBERES Pulmonary Biobank Platform; <sup>3</sup>CUN=Clinica Universidad de Navarra.

**Table S2.** Conditions for protein detection by IHC in formalin fixed paraffin embedded lung cancer samples.

<b>Protein</b>	<b>Reference</b>	<b>Host<sup>1</sup></b>	<b>Class<sup>2</sup></b>	<b>Pre-treatment<sup>3</sup></b>	<b>Dilution</b>	<b>Detection method</b>
BRCA1	Genetex (GTX70113)	M	M	PT-CIT pH6 (20 min 95 °C)	1:500	EnVision M
CDC6	Santa Cruz (sc-56273)	M	M	PT-EDTA pH9 (20 min 95 °C)	1:20	EnVision M
LIG1	Areta International	M	M	PT-EDTA pH9 (20 min 95 °C)	1:500	EnVision M
QKI	Sigma (HPA019123)	R	P	PT-EDTA pH9 (20 min 95 °C)	1:500	EnVision R
RAD51	Calbiochem (PC130)	R	P	PT-EDTA pH9 (20 min 95 °C)	1:100	EnVision R
RAE1	Genetex (EPR6923)	R	M	PT-CIT pH6 (20 min 95 °C)	1:250	EnVision R
RRM2	Sigma (WH0006241M1)	M	M	PT-CIT pH6 (20 min 95 °C)	1:3000	EnVision M
SIRT2	Santa Cruz (sc-28298)	M	M	PT-CIT pH6 (20 min 95 °C)	1:50	EnVision M
SLC2A1	Proteintech (21829-1-AP)	R	P	PT-CIT pH6 (20 min 95 °C)	1:1000	EnVision R
SNRPE	Proteintech (20407-1-AP)	R	P	PT-CIT pH6 (20 min 95 °C)	1:200	EnVision R
SRSF1	Zymed (32-4600)	M	M	PT-EDTA pH9 (20 min 95 °C)	1:200	EnVision M
STC1	Santa Cruz (sc-14346)	G	P	PT-CIT pH6 (20 min 95 °C)	1:100	Streptavidin HRP

<sup>1</sup>**M:** Mouse, **R:** Rabbit, **G:** Goat; <sup>2</sup>**M:** Monoclonal, **P:** Polyclonal; <sup>3</sup>**PT-CIT:** PT-linker buffer citrate (ThermoScientific), **PT-EDTA:** PT-linker buffer Tris EDTA (ThermoScientific).

**Table S3.** *P* values obtained after survival analysis in the microarray datasets.<sup>1</sup>

Gene	Survival analysis	Bild <sup>a</sup>	Lee <sup>b</sup>	Director's Consortium <sup>c</sup>	Okayama <sup>d</sup>	Tomida <sup>e</sup>	Wilkerson <sup>f</sup>	Larsen <sup>g</sup>	Raponi <sup>h</sup>	Wilkerson <sup>i</sup>
<i>ADARB1</i>	DFS		0.580	<b>0.013</b>	0.345					0.820
	OS	0.541		<b>0.013</b>	0.249	0.275	0.929	0.437	0.721	0.885
<i>AGFG1</i>	DFS		0.893	0.443	<b>0.001</b>					0.829
	OS	0.707		0.809	<b>0.001</b>	0.133	0.604	0.353	0.221	0.920
<i>BAG1</i>	DFS		0.944	0.863	0.552					0.585
	OS	0.874		0.466	0.693	0.327	0.410	0.217	0.394	0.836
<i>BRCA1</i>	DFS		0.109	<b>0.001</b>	<b>0.004</b>					0.486
	OS	0.583		<b>0.016</b>	<b>0.004</b>	<b>0.001</b>	0.591	0.117	0.425	0.329
<i>CBX3</i>	DFS		<b>0.092</b>	0.083	0.775					0.226
	OS	0.271		0.092	0.586	<b>0.022</b>	0.171	0.460	0.398	0.119
<i>CDC6</i>	DFS		0.131	<b>0.016</b>	<b>&lt;0.001</b>					<b>0.093</b>
	OS	0.552		<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>0.003</b>	0.661	0.518	0.165	<b>0.085</b>
<i>CDK2API</i>	DFS		0.885	0.938	0.950					0.406
	OS	0.781		0.986	0.759	0.159	0.981	0.158	0.256	0.208
<i>ERBB3</i>	DFS		<b>0.013</b>	<b>0.001</b>	0.695					0.883
	OS	0.288		0.193	0.896	0.236	0.595	0.183	0.895	0.881
<i>FUT3</i>	DFS		0.648	0.540	0.728					0.502
	OS	0.621		0.525	0.187	0.234	0.752	0.172	0.173	0.621
<i>IL11</i>	DFS		0.463	<b>0.005</b>	0.154					0.616
	OS	<b>0.007</b>		<b>0.099</b>	0.744	0.755	0.398	0.723	0.281	0.876
<i>INHA</i>	DFS		0.236	<b>0.028</b>	0.818					0.694
	OS	0.690		<b>0.070</b>	0.201	<b>0.037</b>	0.402	<b>0.050</b>	0.970	0.708
<i>LCK</i>	DFS		<b>0.047</b>	<b>0.017</b>	0.721					0.974
	OS	0.217		0.137	0.898	<b>0.036</b>	0.145	<b>0.010</b>	0.310	0.959
<i>LIG1</i>	DFS		0.519	<b>0.081</b>	0.654					0.131
	OS	<b>0.075</b>		0.376	0.691	0.727	0.989	0.408	0.790	0.236
<i>MARS</i>	DFS		0.407	<b>0.041</b>	<b>&lt;0.001</b>					0.447
	OS	0.121		0.225	<b>0.002</b>	0.158	0.399	0.207	0.553	0.309
<i>QKI</i>	DFS		<b>0.001</b>	0.481	<b>0.012</b>					0.270
	OS	0.140		0.216	<b>0.062</b>	0.993	0.613	0.248	<b>0.034</b>	0.187
<i>RAD51</i>	DFS		0.144	<b>0.069</b>	<b>&lt;0.001</b>					0.324
	OS	0.428		<b>0.043</b>	<b>0.001</b>	<b>0.003</b>	0.257	0.532	0.529	0.197
<i>RAE1</i>	DFS		0.430	0.119	<b>0.076</b>					0.411
	OS	0.995		<b>0.053</b>	0.158	<b>0.015</b>	<b>0.078</b>	0.663	0.322	0.639
<i>RND3</i>	DFS		0.764	0.939	0.179					0.708
	OS	0.826		<b>0.007</b>	0.753	0.216	<b>0.069</b>	0.274	0.327	0.436
<i>RRM2</i>	DFS		0.792	<b>0.093</b>	<b>&lt;0.001</b>					0.387
	OS	0.506		<b>0.001</b>	<b>0.009</b>	<b>0.002</b>	<b>0.086</b>	0.108	0.261	0.252
<i>SERPINE1</i>	DFS		0.171	0.728	0.658					0.877
	OS	<b>0.025</b>		0.634	<b>0.068</b>	0.298	0.609	0.577	0.634	0.733
<i>SH3BGR</i>	DFS		0.324	0.490	0.246					0.790
	OS	0.731		0.604	0.212	0.850	0.546	0.782	0.951	0.840
<i>SIRT2</i>	DFS		0.639	0.618	0.140					0.526
	OS	<b>0.098</b>		<b>0.096</b>	0.765	<b>0.055</b>	0.424	0.573	0.849	0.150
<i>SLC2A1</i>	DFS		0.415	<b>0.011</b>	<b>&lt;0.001</b>					0.532
	OS	0.931		<b>0.013</b>	<b>&lt;0.001</b>	<b>0.033</b>	<b>0.040</b>	0.372	0.182	0.935
<i>SNRPB</i>	DFS		0.478	<b>0.009</b>	<b>0.001</b>					0.123
	OS	0.834		<b>0.064</b>	<b>0.005</b>	<b>&lt;0.001</b>	0.243	0.203	<b>0.094</b>	0.113
<i>SNRPE</i>	DFS		0.580	0.555	0.834					0.673
	OS	0.771		<b>0.088</b>	0.384	<b>0.009</b>	0.310	0.442	0.118	0.883
<i>SRSF1</i>	DFS		0.303	<b>0.055</b>	0.803					0.956
	OS	0.613		<b>0.035</b>	0.621	<b>0.039</b>	0.590	0.196	0.207	0.492
<i>STC1</i>	DFS		0.167	<b>0.059</b>	<b>0.002</b>					0.506
	OS	<b>0.015</b>		<b>0.008</b>	<b>0.001</b>	<b>0.018</b>	0.369	0.633	<b>0.069</b>	0.268
<i>TMSB4X</i>	DFS		NA	NA	NA					NA
	OS	0.715				0.259	NA	NA	<b>0.019</b>	NA
<i>WNT3A</i>	DFS		NA	NA	NA					0.767
	OS	NA				0.286	0.364	0.372	NA	0.747

<sup>1</sup>Significant *P* values or with a strong trend (*P*<0.1) in the Kaplan-Meier survival curves stratifying by median are shown in bold. <sup>a</sup>Bild GSE3141; <sup>b</sup>Lee GSE8894; <sup>c</sup>Director's Consortium GSE68465; <sup>d</sup>Okayama GSE31210;

<sup>e</sup>Tomida GSE13213; <sup>f</sup>Wilkerson GSE26939; <sup>g</sup>Larsen GSE5882; <sup>h</sup>Raponi GSE4573; <sup>i</sup>Wilkerson GSE17710..

**Table S4.** Summary of the strategy conducted for gene selection.

Gene	RNA prognostic value <sup>1</sup>	Commercial antibody available for WB and IHC	Validated antibody	Selected
<i>ADARB1</i>	Low			
<i>AGFG1</i>	Low			
<i>BAG1</i>	None			
<i>BRCA1</i>	High	Yes (Genetex: GTX70113, Calbiochem OP92, Genetex GTX70111, Novus NBP1-41186)	Yes (Genetex: GTX70113)	Yes
<i>CBX3</i>	Medium	No		
<i>CDC6</i>	High	Yes (Santa Cruz: SC-56273)	Yes (Santa Cruz: SC-56273)	Yes
<i>CDK2AP1</i>	None			
<i>ERBB3</i>	Medium	Yes (Santa Cruz SC415, Cell Signaling 12708, Abnova H0002065)	No	
<i>FUT3</i>	None			
<i>IL11</i>	Medium	No		
<i>INHA</i>	High	Yes (Invitrogen PA5-32452, Santa Cruz SC30146, Bios BS1032, Atlas 48834)	No	
<i>LCK</i>	High	No		
<i>LIG1</i>	Medium	Yes (Areta International)	Yes (Areta International)	Yes
<i>MARS</i>	Medium	Yes (Thermo Scientific: PA5-14997)	No	
<i>QKI</i>	High	Yes (Sigma: HPA019123)	Yes (Sigma: HPA019123)	Yes
<i>RAD51</i>	High	Yes (Calbiochem: PC130)	Yes (Calbiochem: PC130)	Yes
<i>RAE1</i>	High	Yes (Genetex: EPR6923)	Yes (Genetex: EPR6923)	Yes
<i>RND3</i>	Medium	Yes (Millipore 05-723, Proteintech 12534-1-AP)	No	
<i>RRM2</i>	High	Yes (Sigma: WH0006241M1)	Yes (Sigma: WH0006241M1)	Yes
<i>SERPINE1</i>	Medium	No		
<i>SH3BGR</i>	None			
<i>SIRT2</i>	High	Yes (Santa Cruz: sc28298)	Yes (Santa Cruz: sc28298)	Yes
<i>SLC2A1</i>	High	Yes (Proteintech: 21829-1-AP, Invitrogen PA5-16793)	Yes (Proteintech: 21829-1-AP)	Yes
<i>SNRPB</i>	High	No		
<i>SNRPE</i>	Medium	Yes (Proteintech: 20407-1-AP)	Yes (Proteintech: 20407-1-AP)	Yes
<i>SRSF1</i>	Medium	Yes (Zymed: 32-4600)	Yes (Zymed: 32-4600)	Yes
<i>STC1</i>	High	Yes (Santa Cruz: sc14346)	Yes (Santa Cruz: sc14346)	Yes
<i>TMSB4X</i>	Low			
<i>WNT3A</i>	None			

<sup>1</sup>High: significant P value or strong trend in the Kaplan-Meier survival curves in at least three different databases. Medium: significant P value in at least two different databases. Low: significant P value in at least one database. None: no apparent association.

**Table S5.** Proteins finally selected for IHC study and their specific subcellular locations in human cell lines and tissue samples.

<b>Protein</b>	<b>Nucleus</b>	<b>Cytoplasm</b>	<b>Membrane</b>
<b>BRCA1</b>	Yes		
<b>CDC6</b>	Yes	Yes	
<b>LIG1</b>	Yes		
<b>QKI</b>	Yes	Yes	
<b>RAD51</b>	Yes	Yes	
<b>RAE1</b>	Yes	Yes	
<b>RRM2</b>		Yes	
<b>SIRT2</b>	Yes	Yes	
<b>SLC2A1</b>		Yes	Yes
<b>SNRPE</b>	Yes		
<b>SRSF1</b>	Yes		
<b>STC1</b>	Yes	Yes	

**Table S6.** C-index values generated in the internal validation of the prognostic signature by bootstrap & shrinkage method for DFS.

Sample	Observed C-index	Validated C-index	Shrinkage	Sample	Observed C-index	Validated C-index	Shrinkage
Original	0.6257	0.6257	0.0000	Bootstrap 51	0.6140	0.6311	-0.0171
Bootstrap 1	0.6275	0.6293	-0.0019	Bootstrap 52	0.5930	0.6118	-0.0188
Bootstrap 2	0.6153	0.6183	-0.0030	Bootstrap 53	0.6643	0.6198	0.0446
Bootstrap 3	0.6172	0.6212	-0.0040	Bootstrap 54	0.6284	0.6299	-0.0014
Bootstrap 4	0.6473	0.6195	0.0278	Bootstrap 55	0.6190	0.6072	0.0118
Bootstrap 5	0.6440	0.6166	0.0273	Bootstrap 56	0.5999	0.6213	-0.0214
Bootstrap 6	0.5846	0.6333	-0.0487	Bootstrap 57	0.6447	0.6272	0.0175
Bootstrap 7	0.6125	0.6280	-0.0155	Bootstrap 58	0.6254	0.6272	-0.0017
Bootstrap 8	0.5789	0.5712	0.0076	Bootstrap 59	0.6243	0.6122	0.0121
Bootstrap 9	0.6264	0.6201	0.0063	Bootstrap 60	0.6100	0.6194	-0.0094
Bootstrap 10	0.6246	0.6246	0.0000	Bootstrap 61	0.6494	0.6149	0.0345
Bootstrap 11	0.6306	0.6288	0.0018	Bootstrap 62	0.6177	0.6153	0.0024
Bootstrap 12	0.5978	0.6147	-0.0170	Bootstrap 63	0.6057	0.6051	0.0006
Bootstrap 13	0.6446	0.6159	0.0288	Bootstrap 64	0.6492	0.6279	0.0213
Bootstrap 14	0.6523	0.6268	0.0256	Bootstrap 65	0.6610	0.6254	0.0356
Bootstrap 15	0.6638	0.6231	0.0407	Bootstrap 66	0.6753	0.6364	0.0389
Bootstrap 16	0.6024	0.5801	0.0223	Bootstrap 67	0.6564	0.6144	0.0420
Bootstrap 17	0.6499	0.6320	0.0180	Bootstrap 68	0.6407	0.6254	0.0153
Bootstrap 18	0.6717	0.6324	0.0393	Bootstrap 69	0.5930	0.6169	-0.0239
Bootstrap 19	0.6516	0.6256	0.0260	Bootstrap 70	0.6546	0.6218	0.0328
Bootstrap 20	0.6315	0.6076	0.0239	Bootstrap 71	0.6345	0.6232	0.0112
Bootstrap 21	0.6104	0.6182	-0.0078	Bootstrap 72	0.5971	0.6315	-0.0344
Bootstrap 22	0.6539	0.6278	0.0261	Bootstrap 73	0.6268	0.6300	-0.0033
Bootstrap 23	0.6297	0.6337	-0.0040	Bootstrap 74	0.5847	0.6266	-0.0418
Bootstrap 24	0.6326	0.6213	0.0113	Bootstrap 75	0.6316	0.6272	0.0044
Bootstrap 25	0.6483	0.6164	0.0319	Bootstrap 76	0.6307	0.6250	0.0057
Bootstrap 26	0.6093	0.6247	-0.0154	Bootstrap 77	0.6564	0.6155	0.0409
Bootstrap 27	0.6274	0.6268	0.0006	Bootstrap 78	0.6609	0.6280	0.0329
Bootstrap 28	0.6314	0.6257	0.0057	Bootstrap 79	0.6234	0.6236	-0.0002
Bootstrap 29	0.6594	0.6194	0.0400	Bootstrap 80	0.5593	0.5693	-0.0099
Bootstrap 30	0.6683	0.6210	0.0473	Bootstrap 81	0.6314	0.6161	0.0153
Bootstrap 31	0.6418	0.5971	0.0448	Bootstrap 82	0.6243	0.6330	-0.0087
Bootstrap 32	0.6256	0.6016	0.0240	Bootstrap 83	0.6582	0.6220	0.0362
Bootstrap 33	0.6712	0.6277	0.0435	Bootstrap 84	0.6406	0.6389	0.0017
Bootstrap 34	0.6312	0.6278	0.0035	Bootstrap 85	0.5948	0.6274	-0.0326
Bootstrap 35	0.6129	0.6251	-0.0122	Bootstrap 86	0.7015	0.6227	0.0788
Bootstrap 36	0.6555	0.6287	0.0269	Bootstrap 87	0.6847	0.6344	0.0504
Bootstrap 37	0.6540	0.6174	0.0366	Bootstrap 88	0.6567	0.6183	0.0384
Bootstrap 38	0.6616	0.6323	0.0292	Bootstrap 89	0.5949	0.5982	-0.0034
Bootstrap 39	0.6285	0.6072	0.0213	Bootstrap 90	0.5955	0.6168	-0.0213
Bootstrap 40	0.6611	0.6155	0.0455	Bootstrap 91	0.5892	0.6101	-0.0209
Bootstrap 41	0.6076	0.6063	0.0014	Bootstrap 92	0.6368	0.6271	0.0097
Bootstrap 42	0.6822	0.6262	0.0560	Bootstrap 93	0.6399	0.6072	0.0327
Bootstrap 43	0.6456	0.6246	0.0210	Bootstrap 94	0.6568	0.6238	0.0330
Bootstrap 44	0.6186	0.6273	-0.0088	Bootstrap 95	0.6132	0.5946	0.0186
Bootstrap 45	0.6264	0.6230	0.0034	Bootstrap 96	0.5997	0.6169	-0.0172
Bootstrap 46	0.6638	0.6275	0.0363	Bootstrap 97	0.6743	0.6176	0.0567
Bootstrap 47	0.6254	0.6101	0.0152	Bootstrap 98	0.6605	0.6337	0.0268
Bootstrap 48	0.6069	0.6245	-0.0176	Bootstrap 99	0.6675	0.6302	0.0373
Bootstrap 49	0.6104	0.6240	-0.0136	Bootstrap 100	0.6785	0.6303	0.0482
Bootstrap 50	0.5595	0.6160	-0.0566	<b>Shrinkage average</b>		<b>0.0123</b>	

**Table S7.** C-index values generated in the internal validation of the prognostic signature by bootstrap & shrinkage method for OS.

Sample	Observed C-index	Validated C-index	Shrinkage	Sample	Observed C-index	Validated C-index	Shrinkage
Original	0.6596	0.6596	0.0000	Bootstrap 51	0.7053	0.6641	0.0412
Bootstrap 1	0.7021	0.6737	0.0284	Bootstrap 52	0.6571	0.6639	-0.0068
Bootstrap 2	0.6582	0.6661	-0.0079	Bootstrap 53	0.7299	0.6702	0.0597
Bootstrap 3	0.6795	0.6773	0.0022	Bootstrap 54	0.6767	0.6560	0.0207
Bootstrap 4	0.6824	0.6636	0.0188	Bootstrap 55	0.6898	0.6551	0.0346
Bootstrap 5	0.6826	0.6566	0.0261	Bootstrap 56	0.6191	0.6686	-0.0494
Bootstrap 6	0.6154	0.6623	-0.0469	Bootstrap 57	0.6783	0.6619	0.0164
Bootstrap 7	0.6421	0.6506	-0.0085	Bootstrap 58	0.6885	0.6658	0.0227
Bootstrap 8	0.6059	0.6536	-0.0477	Bootstrap 59	0.6601	0.6584	0.0017
Bootstrap 9	0.6403	0.6588	-0.0185	Bootstrap 60	0.6840	0.6603	0.0237
Bootstrap 10	0.6901	0.6717	0.0184	Bootstrap 61	0.6617	0.6642	-0.0025
Bootstrap 11	0.6908	0.6672	0.0236	Bootstrap 62	0.7285	0.6713	0.0572
Bootstrap 12	0.6990	0.6523	0.0466	Bootstrap 63	0.6912	0.6448	0.0464
Bootstrap 13	0.6808	0.6670	0.0138	Bootstrap 64	0.6710	0.6740	-0.0029
Bootstrap 14	0.6663	0.6669	-0.0005	Bootstrap 65	0.7372	0.6707	0.0665
Bootstrap 15	0.6665	0.6749	-0.0084	Bootstrap 66	0.6901	0.6734	0.0167
Bootstrap 16	0.5903	0.6428	-0.0525	Bootstrap 67	0.6707	0.6665	0.0041
Bootstrap 17	0.7131	0.6766	0.0365	Bootstrap 68	0.6804	0.6763	0.0042
Bootstrap 18	0.6552	0.6527	0.0025	Bootstrap 69	0.6646	0.6438	0.0208
Bootstrap 19	0.6909	0.6667	0.0242	Bootstrap 70	0.6890	0.6642	0.0248
Bootstrap 20	0.7068	0.6483	0.0585	Bootstrap 71	0.6870	0.6757	0.0113
Bootstrap 21	0.6460	0.6633	-0.0173	Bootstrap 72	0.6435	0.6657	-0.0222
Bootstrap 22	0.6654	0.6542	0.0112	Bootstrap 73	0.6623	0.6608	0.0015
Bootstrap 23	0.6624	0.6499	0.0125	Bootstrap 74	0.6518	0.6670	-0.0153
Bootstrap 24	0.6810	0.6707	0.0103	Bootstrap 75	0.6743	0.6697	0.0046
Bootstrap 25	0.7351	0.6791	0.0559	Bootstrap 76	0.6569	0.6675	-0.0107
Bootstrap 26	0.6931	0.6792	0.0139	Bootstrap 77	0.7009	0.6548	0.0461
Bootstrap 27	0.7060	0.6715	0.0345	Bootstrap 78	0.7469	0.6596	0.0873
Bootstrap 28	0.6726	0.6711	0.0015	Bootstrap 79	0.6873	0.6702	0.0171
Bootstrap 29	0.6920	0.6619	0.0300	Bootstrap 80	0.6277	0.6688	-0.0412
Bootstrap 30	0.7091	0.6786	0.0304	Bootstrap 81	0.6965	0.6807	0.0157
Bootstrap 31	0.6682	0.6383	0.0299	Bootstrap 82	0.6736	0.6677	0.0059
Bootstrap 32	0.7100	0.6647	0.0454	Bootstrap 83	0.6864	0.6673	0.0191
Bootstrap 33	0.7261	0.6677	0.0584	Bootstrap 84	0.6833	0.6743	0.0090
Bootstrap 34	0.6445	0.6436	0.0009	Bootstrap 85	0.7100	0.6590	0.0510
Bootstrap 35	0.6712	0.6669	0.0044	Bootstrap 86	0.7156	0.6586	0.0571
Bootstrap 36	0.6788	0.6824	-0.0036	Bootstrap 87	0.7016	0.6751	0.0266
Bootstrap 37	0.7251	0.6730	0.0521	Bootstrap 88	0.6559	0.6599	-0.0039
Bootstrap 38	0.6832	0.6660	0.0172	Bootstrap 89	0.6577	0.6642	-0.0065
Bootstrap 39	0.6580	0.6479	0.0101	Bootstrap 90	0.6422	0.6587	-0.0165
Bootstrap 40	0.6487	0.6529	-0.0042	Bootstrap 91	0.6688	0.6641	0.0048
Bootstrap 41	0.6638	0.6542	0.0096	Bootstrap 92	0.7136	0.6739	0.0397
Bootstrap 42	0.7077	0.6679	0.0398	Bootstrap 93	0.6840	0.6751	0.0089
Bootstrap 43	0.6177	0.6664	-0.0486	Bootstrap 94	0.6742	0.6693	0.0049
Bootstrap 44	0.6950	0.6757	0.0194	Bootstrap 95	0.7050	0.6791	0.0259
Bootstrap 45	0.7013	0.6677	0.0336	Bootstrap 96	0.6660	0.6692	-0.0032
Bootstrap 46	0.7009	0.6615	0.0394	Bootstrap 97	0.7637	0.6698	0.0938
Bootstrap 47	0.7002	0.6768	0.0234	Bootstrap 98	0.7123	0.6571	0.0552
Bootstrap 48	0.6759	0.6768	-0.0009	Bootstrap 99	0.7063	0.6652	0.0411
Bootstrap 49	0.6886	0.6668	0.0218	Bootstrap 100	0.6834	0.6702	0.0131
Bootstrap 50	0.6096	0.6604	-0.0508	<b>Shrinkage average</b>		<b>0.0149</b>	

**Table S8.** Univariate and multivariate Cox proportional hazards analysis of PI score and clinicopathological parameters in CIBERES-CUN cohort (early stages).

Validation cohort	CUN n (%)	DFS <sup>1,2</sup>				CIBERES -CUN n (%)	OS <sup>3</sup>			
		Univariate analysis		Multivariate analysis			Univariate analysis		Multivariate analysis	
		HR (95% CI)	P value	HR (95% CI)	P value		HR (95% CI)	P value	HR (95% CI)	P value
<b>PI<sup>4</sup></b>		2.13 (0.99-4.57)	<b>0.053</b>	3.25 (1.26-8.41)	<b>0.015</b>		2.17 (1.18-3.98)	<b>0.013</b>	2.10 (1.12-3.93)	<b>0.021</b>
<b>Stage</b>			0.166		0.474			0.166		<b>0.229</b>
<b>IA</b>	13 (40.6%)	1		1		33 (33.3%)	1		1	
<b>IB</b>	6 (18.8%)	5.83 (1.06-32.04)	<b>0.042</b>	4.23 (0.70-25.62)	0.117	24 (24.2%)	1.38 (0.42-4.54)	0.594	1.16 (0.35-3.82)	0.814
<b>IIA</b>	2 (6.3%)	0 (0.00-0.00)	0.989	0 (0.00-0.00)	0.990	6 (6.1%)	1.53 (0.18-12.73)	0.696	1.12 (0.13-9.46)	0.919
<b>IIB</b>	11 (34.4%)	5.79 (1.15-29.28)	<b>0.034</b>	2.69 (0.31-23.68)	0.373	36 (36.4%)	2.84 (1.08-7.53)	<b>0.035</b>	2.47 (0.93-6.59)	0.071
<b>Gender</b>			0.153					0.933		
<b>Male</b>	27 (84.4%)	1				73 (73.7%)	1			
<b>Female</b>	5 (15.6%)	2.68 (0.68-10.33)				26 (26.3%)	1.04 (0.41-2.61)			
<b>Age (years)</b>			0.624		0.187			0.584		
<b>&lt;65</b>	20 (62.5%)	1		1		59 (59.6%)	1			
<b>≥65</b>	12 (37.5%)	1.33 (0.42-4.22)		3.13 (0.58-17.06)		40 (40.4%)	1.25 (0.57-2.75)			
<b>Adjuvant treatment</b>			0.101							
<b>No</b>	20 (62.5%)	1								
<b>Yes</b>	12 (37.5%)	2.60 (0.83-8.17)								
<b>Tobacco</b>			0.396							
<b>Never</b>	5 (15.6%)	1								
<b>Former</b>	24 (75.0%)	0.42 (0.11-1.63)	0.212							
<b>Current</b>	3 (9.4%)	0.30 (0.03-2.94)	0.298							

<sup>1</sup>Events/n = 12/32. <sup>2</sup>Complete data available for CUN patients. <sup>3</sup>Events/n = 25/99. <sup>4</sup>PI: prognostic index.



**Table S9.** Prognostic value of PI and stage in univariate and bivariate models for MDA cohort.

MDA cohort				
	DFS		OS	
	LR	P value	LR	P value
<b>Stage</b>	53.449	<b>&lt;0.001</b>	24.427	<b>&lt;0.001</b>
<b>Stage &amp; PI</b>	66.566	<b>&lt;0.001</b>	44.063	<b>&lt;0.001</b>
<b>LR<sup>1</sup> improvement</b>	13.385	<b>&lt;0.001</b>	19.950	<b>&lt;0.001</b>

<sup>1</sup>LR: Likelihood ratio

**Table S10.** Univariate and multivariate Cox proportional hazards analysis of CPI score and clinicopathological parameters for DFS and OS in MDA cohort.

MDA Cohort	n (%)	DFS <sup>1</sup>				OS <sup>2</sup>			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
<b>CPI<sup>3</sup></b>		2.72 (2.05-3.60)	<b>&lt;0.001</b>	2.95 (2.13-4.08)	<b>&lt;0.001</b>	2.67 (1.97-3.63)	<b>&lt;0.001</b>	2.56 (1.88-3.49)	<b>&lt;0.001</b>
<b>Gender</b>			0.132		0.899		<b>0.009</b>		0.132
<b>Male</b>	92 (40.7 %)	1		1		1		1	
<b>Female</b>	134 (59.3%)	0.73 (0.49-1.10)		1.03 (0.67-1.58)		0.55 (0.35-0.86)		0.71 (0.45-1.11)	
<b>Age</b>			0.910				0.434		
<b>&lt;65</b>	29 (12.8%)	1				1			
<b>≥65</b>	197 (87.2%)	1.04 (0.57-1.90)				1.34 (0.64-2.78)			
<b>Adjuvant treatment</b>			0.092		0.391		0.838		
<b>No</b>	130 (57.5%)	1		1		1			
<b>Yes</b>	83 (36.8%)	1.53 (1.00-2.33)		0.82 (0.51-1.30)		1.05 (0.65-1.69)			
<b>Unknown</b>	8 (5.7%)								
<b>Tobacco</b>			0.764				0.683		
<b>Never</b>	39 (17.3%)	1				1			
<b>Former</b>	107 (47.3%)	1.15 (0.63-2.10)	0.648			0.82 (0.45-1.51)	0.523		
<b>Current</b>	80 (35.4%)	1.26 (0.68-2.34)	0.469			1.00 (0.54-1.87)	0.992		

<sup>1</sup>Events/n= 93/226 in univariate and multivariate analysis (DFS). <sup>2</sup>Events/n= 77/226 in univariate and multivariate analysis (OS). <sup>3</sup>CPI: combined prognostic index.

**Table S11.** Univariate and multivariate Cox proportional hazards analysis of CPI and clinicopathological parameters for OS in CIBERES-CUN cohort.

Validation cohort	CUN n (%)	DFS <sup>1,2</sup>				CIBERES-CUN n (%)	OS <sup>3</sup>			
		Univariate analysis		Multivariate analysis			Univariate analysis		Multivariate analysis	
		HR (95% CI)	P value	HR (95% CI)	P value		HR (95% CI)	P value	HR (95% CI)	P value
<b>CPI<sup>4</sup></b>		2.10 (1.27-3.47)	<b>0.004</b>	2.17 (1.20-3.92)	<b>0.011</b>		2.35 (1.57-3.52)	<b>&lt;0.001</b>	2.36 (1.58-3.51)	<b>&lt;0.001</b>
<b>Gender</b>			0.152		0.054			0.709		
<b>Male</b>	33 (84.6%)	1		1		86 (75.4%)	1			
<b>Female</b>	6 (15.4%)	2.31 (0.74-7.27)		3.37 (0.98-11.63)		28 (24.6%)	0.85 (0.37-1.96)			
<b>Age (years)</b>			0.885		0.587			0.176		0.114
<b>&lt;65</b>	24 (61.5%)	1		1		65 (57.0%)	1		1	
<b>≥65</b>	15 (38.5%)	0.93 (0.34-2.51)		1.35 (0.46-4.013)		49 (43.0%)	1.57 (0.82-3.03)		1.71 (0.88-3.30)	
<b>Adjuvant treatment</b>			0.047							
<b>No</b>	22 (56.4%)	1								
<b>Yes</b>	17 (43.6%)	2.70 (1.01-7.16)								
<b>Tobacco</b>			0.769							
<b>Never</b>	5 (12.8%)	1								
<b>Former</b>	30 (76.9%)	0.62 (0.17-2.23)		0.469						
<b>Current</b>	4 (10.3%)	0.67 (0.11-4.07)		0.662						

<sup>1</sup>Events/n= 17/39. <sup>2</sup>Complete data available for CUN patients. <sup>3</sup>Events/N = 36/114<sup>4</sup>CPI: combined prognostic index