

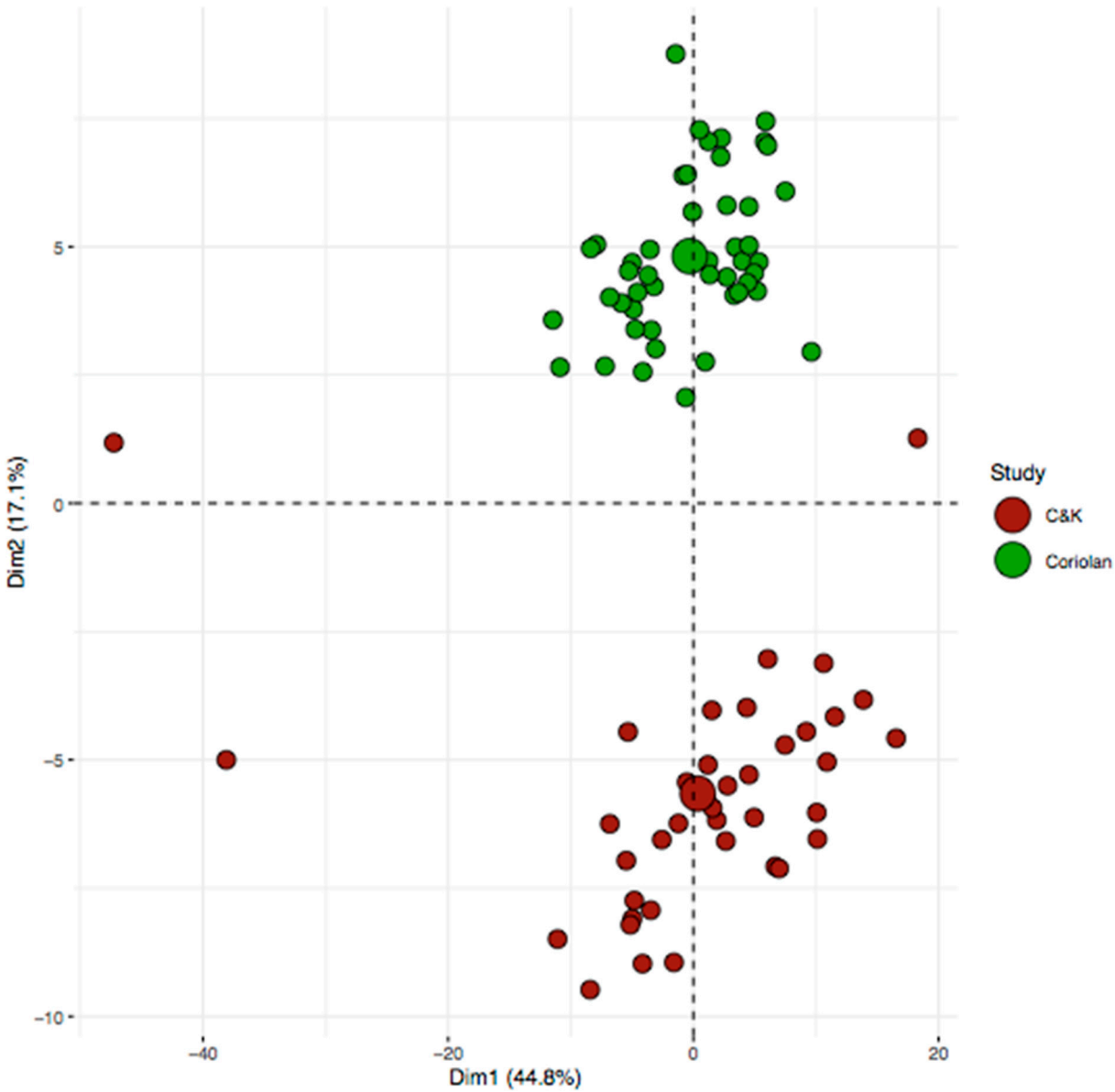
Supplementary files

Table S1. Dilution, range, and sensitivity for cytokines tested by ELISA in the validation cohort

	Dilution		Range	Sensitivity
	Healthy volunteers	Study patients		
IGFBP-1	100x	200x	31.2 pg/mL - 2000 pg/mL	1 pg/mL
IGFBP-2	100x	300x	8.23 pg/mL - 6000 pg/mL	20 pg/mL
SAA	300x	2000x	0.41 ng/mL - 300 ng/mL	0.5 ng/mL
ANG-II	no dilution		31.25 pg/mL - 2000 pg/m	18.75 pg/mL

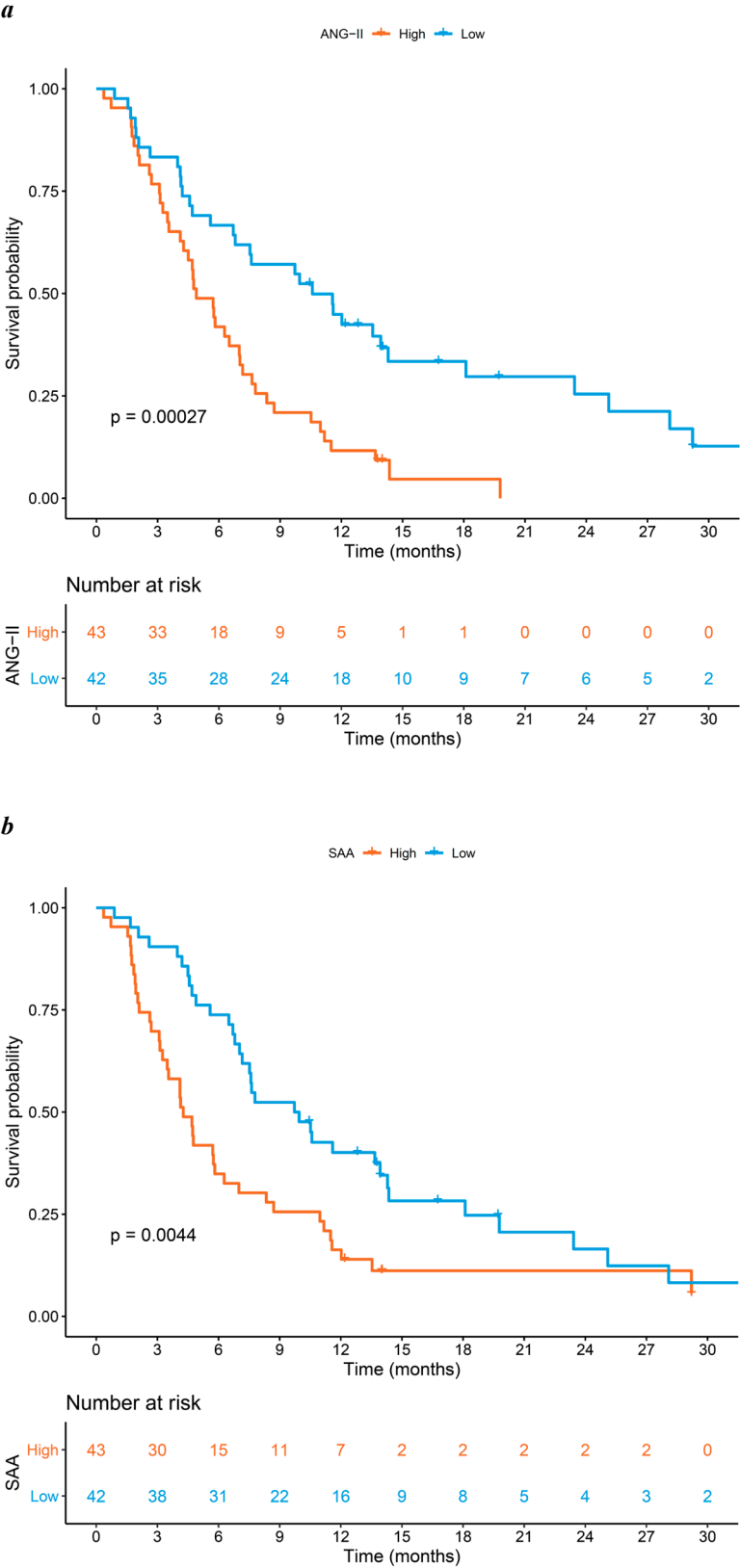
Abbreviations: ANG-II, Angiotensin II; IGFBP-1, insulin-like growth factor-binding protein 1; IGFBP-2, insulin-like growth factor-binding protein 2; SAA, Serum Amyloid A.

Figure S1. Principal component analysis of cytokine expression by source study in the discovery cohort



Abbreviations: C&K, Chronos & Kairos.

Figure S2. Kaplan-Meier curve for overall survival by expression of (a) Angiotensin II and (b) Serum Amyloid A and in the discovery cohort



Abbreviations: ANG-II, Angiotensin II; SAA, Serum Amyloid A.

Table S2. Median values of IGFBP1, IGFBP2, SAA and angiotensin II in patients from the validation cohort and healthy volunteers

	Validation cohort	Healthy volunteers
IGFBP1 (pg/ml) Median	42,821	33,292
IGFBP2 (pg/ml) Median	696,509	508,958
SAA (ng/ml) Median	8,418	1,962
Angiotensin II (pg/ml) Median	703	921

Abbreviations: ANG-II, Angiotensin II; IGFBP-1, insulin-like growth factor-binding protein 1; IGFBP-2, insulin-like growth factor-binding protein 2; SAA, Serum Amyloid A;

Figure S3. Correlation between the cytokines analysed in the validation cohort (Spearman rank correlation)

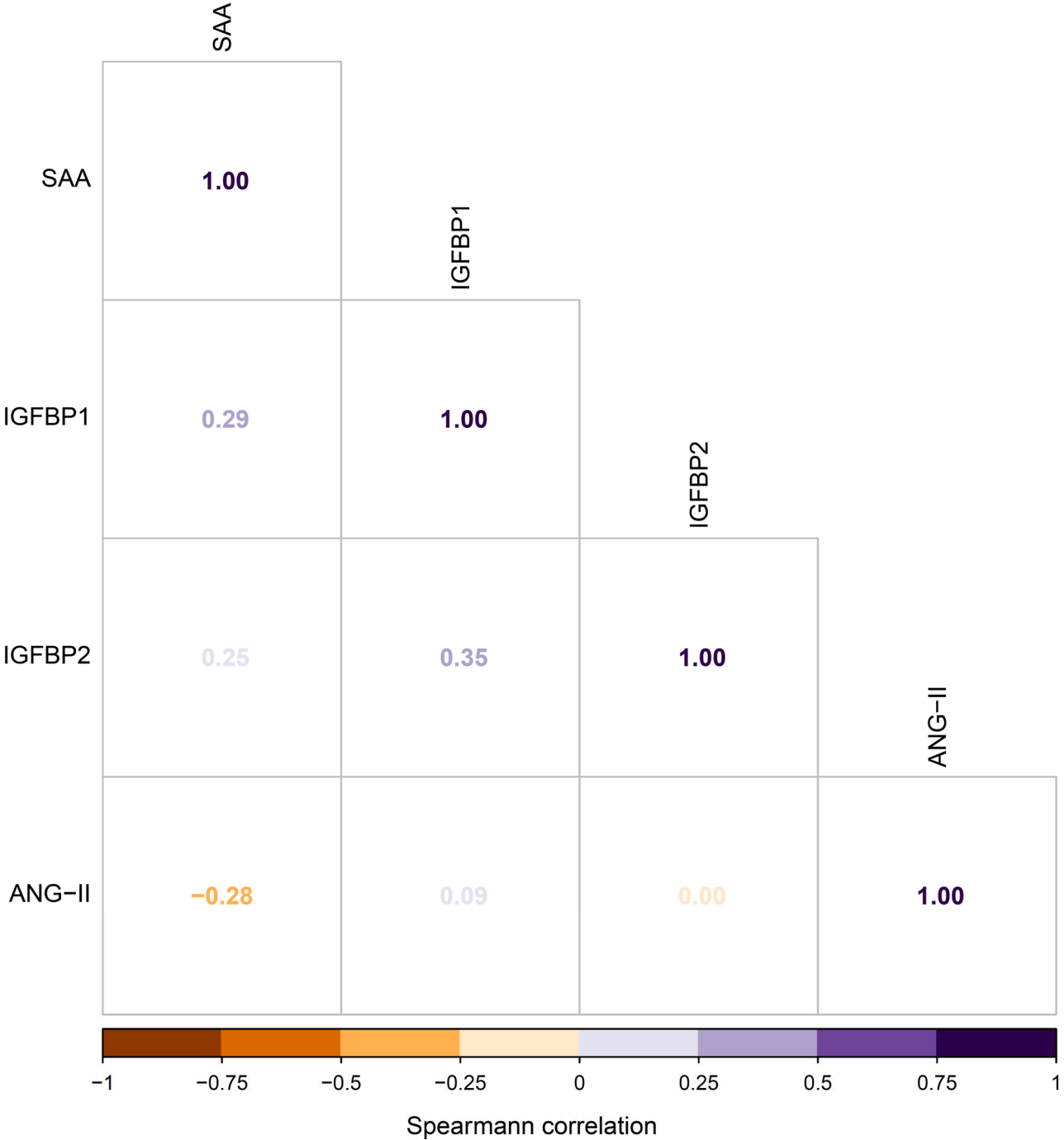
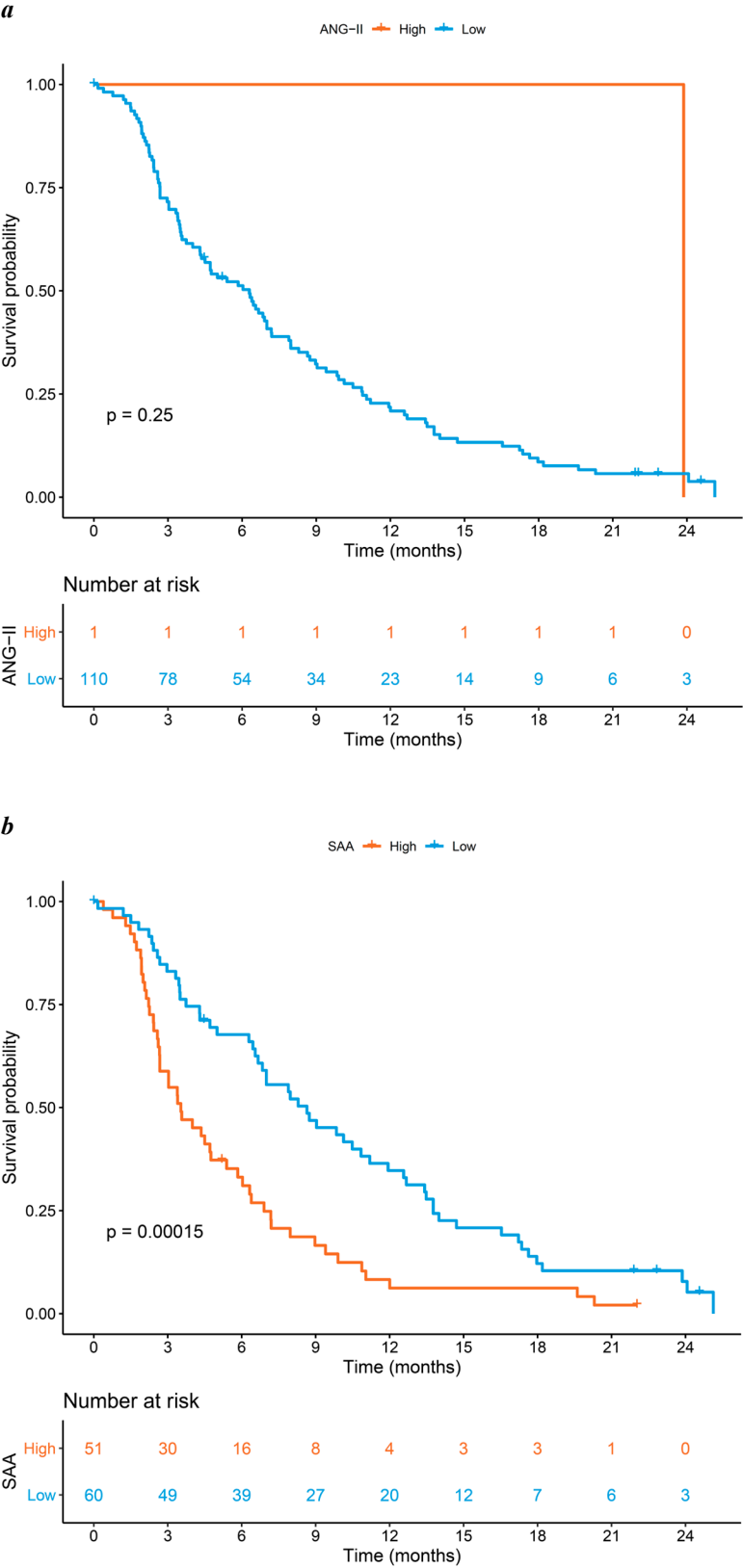


Figure S4. Kaplan-Meier curve for overall survival by expression of (a) Angiotensin II and (b) Serum Amyloid A and in the validation cohort



Abbreviations: ANG-II, Angiotensin II; SAA, Serum Amyloid A.

Table S3. Univariable and multivariable analyses in the validation cohort

Cytokine	Univariable analysis		Multivariable analysis	
	HR (95% CI)	FDR	HR (95% CI)	FDR
IGFBP1	2.04 (1.20-3.45)	0.024	2.70 (1.56-4.76)	0.006
IGFBP2	4.17 (2.08-8.33)	0.001	3.33 (1.61-6.67)	0.008
SAA	2.13 (1.43-3.23)	0.001	1.54 (0.99-2.44)	0.092
IGFBP1 + IGFBP2	2.44 (1.52-4.0)	0.002	3.03 (1.79-5.0)	<0.001

Abbreviations: ANG-II, Angiotensin II; IGFBP-1, insulin-like growth factor-binding protein 1; IGFBP-2, insulin-like growth factor-binding protein 2; SAA, Serum Amyloid A; FDR, false discovery rate; HR, hazard ratio; CI, confidence intervals.

Table S4. Patient characteristics according to the expression of IGFBP-1 and/or IGFBP-2 in the validation cohort

	IGFBP-1 and IGFBP-2 low expression (N=87)	IGFBP-1 and/or IGFBP-2 high expression (N=24)
Age median (IQR)	66 (9)	67 (8)
Sex Male female	53 (60.9%) 34 (39.1%)	13 (54.2%) 11 (45.8%)
ECOG PS 0 ≥1	44 (50.5%) 43 (49.5%)	7 (29.2%) 17 (70.8%)
Primary tumor location Left Right Unknown	61 (70.1%) 15 (17.2%) 11 (12.7%)	13 (54.2%) 5 (20.8%) 6 (25%)
<i>RAS/BRAF</i> status <i>RAS/BRAF</i> mutated <i>RAS/BRAF</i> wild-type Unknown	56 (64.3%) 30 (34.5%) 1 (1.2%)	15 (62.5%) 8 (33%) 1 (4.5%)
N of metastatic sites 1 ≥2	12 (13.8%) 75 (86.2%)	2 (8.4%) 22 (91.6%)
Liver metastasis Present Absent	63 (72.4%) 24 (27.6%)	19 (79.2%) 5 (20.8%)
Peritoneal metastasis Present Absent	15 (17.2%) 72 (82.8%)	6 (25%) 18 (75%)
Baseline ALP Median (IQR)	151 (189)	239 (308)
Baseline CEA Median (IQR)	117 (311)	137 (833)
Time from diagnosis to blood sampling median (IQR)	40 (36)	25 (36.9)

Abbreviations: ALP, alkaline phosphatase; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.