

Supplementary Tables

Dependent: GDF15		unit	value	n (%)	p-value
Age	<70	Mean (sd)	2045.5 (2075.0)	17 (43.6)	0.103
	≥70	Mean (sd)	2869.5 (913.4)	22 (56.4)	
Sex	Female	Mean (sd)	2125.1 (1092.3)	13 (33.3)	0.283
	Male	Mean (sd)	2702.9 (1740.2)	26 (66.7)	
ECOG PS	0-1	Mean (sd)	2356.5 (1043.6)	34 (87.2)	0.110
	≥2	Mean (sd)	3556.2 (3560.4)	5 (12.8)	
Histology	nonsquamous	Mean (sd)	2481.4 (1701.8)	32 (82.1)	0.809
	squamous	Mean (sd)	2642.5 (706.3)	7 (17.9)	
N. of metastatic sites	0-3	Mean (sd)	2575.4 (1635.4)	34 (87.2)	0.505
	>3	Mean (sd)	2067.4 (940.4)	5 (12.8)	
Treatment	CT-ICI	Mean (sd)	2599.7 (1658.5)	27 (73.0)	0.312
	ICI	Mean (sd)	2017.2 (1104.0)	10 (27.0)	
BMI	low	Mean (sd)	4210.6 (3628.3)	4 (10.3)	0.21
	normal	Mean (sd)	2029.4 (900.3)	18 (46.2)	
	over	Mean (sd)	2619.5 (1217.6)	17 (43.6)	
Brain met.	no	Mean (sd)	2684.3 (1623.7)	28 (71.8)	0.273
	yes	Mean (sd)	2067.2 (1368.6)	11 (28.2)	
Liver met.	no	Mean (sd)	2625.9 (1590.0)	35 (89.7)	0.175
	yes	Mean (sd)	1498.5 (895.4)	4 (10.3)	
Lung met.	no	Mean (sd)	2284.2 (1052.4)	19 (48.7)	0.386
	yes	Mean (sd)	2725.1 (1934.3)	20 (51.3)	
PD-L1 expression	<50%	Mean (sd)	2776.8 (1734.0)	26 (72.2)	0.208
	≥50%	Mean (sd)	2017.2 (1104.0)	10 (27.8)	
KRAS	mutated	Mean (sd)	2467.0 (2375.3)	12 (30.8)	0.166
	wild type	Mean (sd)	2529.5 (1088.9)	27 (69.2)	

Table 1S. Baseline characteristics according to GDF15 plasma levels.

Abbreviations: Eastern Cooperative Oncology Group Performance Status, ECOG PS; n., number; met., metastasis

Dependent: cPLIN2		unit	value	n (%)	p-value
Age	<70	Mean (sd)	49.6 (58.0)	17 (43.6)	0.718
	≥70	Mean (sd)	57.9 (78.4)	22 (56.4)	
Sex	Female	Mean (sd)	59.7 (60.9)	13 (33.3)	0.737
	Male	Mean (sd)	51.6 (74.4)	26 (66.7)	
ECOG PS	0-1	Mean (sd)	57.5 (73.7)	34 (87.2)	0.460
	≥2	Mean (sd)	32.5 (20.2)	5 (12.8)	
Histology	nonsquamous	Mean (sd)	52.4 (65.5)	32 (82.1)	0.719
	squamous	Mean (sd)	63.0 (91.2)	7 (17.9)	
N. of metastatic sites	0-3	Mean (sd)	51.3 (63.6)	34 (87.2)	0.497
	>3	Mean (sd)	74.3 (109.1)	5 (12.8)	
Treatment	CT-ICI	Mean (sd)	48.3 (64.2)	27 (73.0)	0.318
	ICI	Mean (sd)	75.0 (88.1)	10 (27.0)	
BMI	low	Mean (sd)	10.6 (4.1)	4 (10.3)	0.394
	normal	Mean (sd)	54.7 (77.0)	18 (46.2)	
	over	Mean (sd)	64.1 (67.8)	17 (43.6)	
Brain met.	no	Mean (sd)	41.7 (54.4)	28 (71.8)	0.071
	yes	Mean (sd)	86.3 (93.9)	11 (28.2)	
Liver met.	no	Mean (sd)	55.0 (71.6)	35 (89.7)	0.844
	yes	Mean (sd)	47.7 (54.5)	4 (10.3)	
Lung met.	no	Mean (sd)	56.8 (76.6)	19 (48.7)	0.831
	yes	Mean (sd)	51.9 (64.0)	20 (51.3)	
PD-L1 expression	<50%	Mean (sd)	48.0 (64.3)	26 (72.2)	0.317
	>50%	Mean (sd)	75.0 (88.1)	10 (27.8)	
KRAS	mutated	Mean (sd)	83.1 (90.3)	12 (30.8)	0.085
	wild type	Mean (sd)	41.5 (55.3)	27 (69.2)	

Table 2S. Baseline characteristics according to Plin2 plasma levels.

Abbreviations: Eastern Cooperative Oncology Group Performance Status, ECOG PS; n., number; met., metastasis

Dependent: FGF21		unit	value	n (%)	p-value
Age	<70	Mean (sd)	390.0 (286.7)	17 (43.6)	0.559
	≥70	Mean (sd)	492.6 (670.8)	22 (56.4)	
Sex	Female	Mean (sd)	685.4 (825.8)	13 (33.3)	0.35
	Male	Mean (sd)	329.1 (251.5)	26 (66.7)	
ECOG PS	0-1	Mean (sd)	397.4 (383.4)	34 (87.2)	0.126
	≥2	Mean (sd)	790.6 (1155.3)	5 (12.8)	
Histology	nonsquamous	Mean (sd)	480.8 (583.2)	32 (82.1)	0.418
	squamous	Mean (sd)	297.1 (145.5)	7 (17.9)	
N. of metastatic sites	0-3	Mean (sd)	481.9 (561.1)	34 (87.2)	0.307
	>3	Mean (sd)	216.7 (204.3)	5 (12.8)	
Treatment	CT-ICI	Mean (sd)	454.8 (600.3)	27 (73.0)	0.970
	ICI	Mean (sd)	446.9 (391.9)	10 (27.0)	
BMI	low	Mean (sd)	427.1 (331.8)	4 (10.3)	0.174
	normal	Mean (sd)	285.5 (176.5)	18 (46.2)	
	over	Mean (sd)	624.6 (749.9)	17 (43.6)	
Brain met.	no	Mean (sd)	518.8 (603.0)	28 (71.8)	0.190
	yes	Mean (sd)	267.2 (233.8)	11 (28.2)	
Liver met.	no	Mean (sd)	448.2 (551.5)	35 (89.7)	0.992
	yes	Mean (sd)	445.2 (417.1)	4 (10.3)	
Lung met.	no	Mean (sd)	586.6 (716.8)	19 (48.7)	0.115
	yes	Mean (sd)	316.1 (218.2)	20 (51.3)	
PD-L1 expression	<50%	Mean (sd)	464.2 (611.5)	26 (72.2)	0.935
	>50%	Mean (sd)	446.9 (391.9)	10 (27.8)	
KRAS	mutated	Mean (sd)	366.8 (296.0)	12 (30.8)	0.963
	wild type	Mean (sd)	483.9 (613.5)	27 (69.2)	

Table 3S. Baseline characteristics according to FGF21 plasma levels.

Abbreviations: Eastern Cooperative Oncology Group Performance Status, ECOG PS; n., number; met., metastasis

Dependent: sRAGE		unit	value	n (%)	p-value
Age	<70	Mean (sd)	596.8 (271.5)	17 (43.6)	0.002
	≥70	Mean (sd)	1160.7 (664.0)	22 (56.4)	
Sex	Female	Mean (sd)	913.4 (795.2)	13 (33.3)	0.991
	Male	Mean (sd)	915.7 (485.7)	26 (66.7)	
ECOG PS	0-1	Mean (sd)	949.4 (628.7)	34 (87.2)	0.352
	≥2	Mean (sd)	680.0 (178.9)	5 (12.8)	
Histology	nonsquamous	Mean (sd)	836.6 (464.6)	32 (82.1)	0.079
	squamous	Mean (sd)	1273.0 (974.8)	7 (17.9)	
N. of metastatic sites	0-3	Mean (sd)	918.7 (635.6)	34 (87.2)	0.918
	>3	Mean (sd)	888.8 (194.6)	5 (12.8)	
Treatment	CT-ICI	Mean (sd)	804.3 (432.3)	27 (73.0)	0.055
	ICI	Mean (sd)	1233.1 (888.6)	10 (27.0)	
BMI	low	Mean (sd)	496.8 (261.0)	4 (10.3)	0.129
	normal	Mean (sd)	828.3 (675.1)	18 (46.2)	
	over	Mean (sd)	1105.0 (505.3)	17 (43.6)	
Brain met.	no	Mean (sd)	988.3 (658.6)	28 (71.8)	0.224
	yes	Mean (sd)	728.1 (352.2)	11 (28.2)	
Liver met.	no	Mean (sd)	947.2 (613.7)	35 (89.7)	0.323
	yes	Mean (sd)	632.2 (329.9)	4 (10.3)	
Lung met.	no	Mean (sd)	948.2 (679.2)	19 (48.7)	0.738
	yes	Mean (sd)	883.2 (520.3)	20 (51.3)	
PD-L1 expression	<50%	Mean (sd)	790.8 (380.2)	26 (72.2)	0.11
	≥50%	Mean (sd)	1233.1 (888.6)	10 (27.8)	
KRAS	mutated	Mean (sd)	670.8 (298.5)	12 (30.8)	0.075
	wild type	Mean (sd)	1023.4 (664.3)	27 (69.2)	

Table 4S. Baseline characteristics according to sRAGE plasma levels.

Abbreviations: Eastern Cooperative Oncology Group Performance Status, ECOG PS; n., number; met., metastasis

Variable 1	Variable 2	Correlation	p-value
Muscle Area	SMI	0.93	<0.0001
Visceral Fat Area	Subcutaneous Fat Area	0.72	<0.0001
NLR	dNLR	0.91	<0.0001
LIPI	dNLR	0.82	<0.0001
LIPI	NLR	0.68	<0.0001
PLR	cPLIN2	-0.66	0.0001
LIPI	LDH	0.62	0.0001
Visceral Fat Area	cPLIN2	0.57	0.0006
LDH	NLR	0.56	0.0008
Subcutaneous Fat Area	cPLIN2	0.55	0.0012
PLR	Visceral Fat Area	-0.53	0.0017
LDH	dNLR	0.52	0.0022
LIPI	sRAGE	-0.47	0.0062
PLR	NLR	0.47	0.0070
sRAGE	GDF15	0.44	0.0125
PLR	FGF21	0.43	0.0138
dNLR	sRAGE	-0.39	0.0297

Variable 1	Variable 2	Correlation	p-value
PLR	Subcutaneous Fat Area	-0.36	0.0421
NLR	cPLIN2	-0.35	0.0479
SMI	FGF21	-0.35	0.0487
Muscle Area	FGF21	-0.35	0.0489
PLR	dNLR	0.34	0.0546
LIPI	SMI	-0.34	0.0570
NLR	sRAGE	-0.33	0.0641
Visceral Fat Area	SMI	0.33	0.0670
PLR	SMI	-0.33	0.0686
Visceral Fat Area	sRAGE	0.31	0.0821
NLR	Subcutaneous Fat Area	-0.31	0.0845
Subcutaneous Fat Area	sRAGE	0.30	0.0907
LDH	sRAGE	-0.30	0.0918
LIPI	Muscle Area	-0.30	0.0948
PLR	Muscle Area	-0.30	0.0955
dNLR	SMI	-0.29	0.1062
Visceral Fat Area	Muscle Area	0.28	0.1145
LDH	cPLIN2	-0.27	0.1314
LDH	PLR	0.26	0.1451

Variable 1	Variable 2	Correlation	p-value
dNLR	Subcutaneous Fat Area	-0.25	0.1614
dNLR	Muscle Area	-0.24	0.1800
Muscle Area	GDF15	-0.24	0.1841
PLR	GDF15	0.24	0.1891
LDH	GDF15	0.24	0.1925
SMI	GDF15	-0.23	0.2035
LDH	SMI	-0.22	0.2275
dNLR	cPLIN2	-0.21	0.2400
LDH	Muscle Area	-0.21	0.2568
NLR	SMI	-0.21	0.2586
dNLR	Visceral Fat Area	-0.20	0.2706
Muscle Area	cPLIN2	-0.19	0.2992
sRAGE	cPLIN2	0.18	0.3140
Visceral Fat Area	FGF21	-0.18	0.3167
LIPI	Subcutaneous Fat Area	-0.18	0.3243
Subcutaneous Fat Area	SMI	0.18	0.3321
NLR	Visceral Fat Area	-0.17	0.3456
LIPI	Visceral Fat Area	-0.17	0.3656
SMI	cPLIN2	-0.16	0.3874

Variable 1	Variable 2	Correlation	p-value
dNLR	GDF15	0.16	0.3896
LDH	Visceral Fat Area	-0.15	0.4169
NLR	Muscle Area	-0.15	0.4248
LIPI	PLR	0.13	0.4628
Subcutaneous Fat Area	FGF21	0.13	0.4927
Subcutaneous Fat Area	Muscle Area	0.12	0.5219
NLR	GDF15	0.11	0.5303
LDH	Subcutaneous Fat Area	-0.11	0.5341
LIPI	cPLIN2	-0.10	0.5756
SMI	sRAGE	0.10	0.5762
LIPI	FGF21	-0.10	0.5981
cPLIN2	GDF15	-0.10	0.5984
LIPI	GDF15	0.07	0.7002
Subcutaneous Fat Area	GDF15	0.07	0.7107
PLR	sRAGE	-0.06	0.7265
Muscle Area	sRAGE	-0.06	0.7490
FGF21	GDF15	0.06	0.7553
LDH	FGF21	-0.05	0.7687
sRAGE	FGF21	0.05	0.7813

Variable 1	Variable 2	Correlation	p-value
dNLR	FGF21	0.04	0.8201
FGF21	cPLIN2	0.02	0.9035
NLR	FGF21	-0.02	0.9274
Visceral Fat Area	GDF15	0.01	0.9563

Table 5S. Correlation between circulating biomarkers, body composition and inflammatory ratios at baseline (T0).

Biomarker	Cut-off (pg/mL)	AUC (ROC)	HR (OS)	p-value (OS)	HR (PFS)	p-value (PFS)
GDF15 (cont)	–		0.98	0.44	1.0	0.972
FGF21 (cont)	–		1.11	0.0428	1.07	0.159
cPLIN2 (cont)	–		0.78	0.544	0.86	0.63
sRAGE (cont)	–		0.93	0.231	0.93	0.106
GDF15 (cat)	1652.5	0.625	1.35	0.579	1.28	0.538
FGF21 (cat)	1507.5	0.4837	1.19	0.741	0.85	0.674
cPLIN2 (cat)	38.84	0.5272	1.68	0.321	2.21	0.0692
sRAGE (cat)	1065.5	0.6712	7.38	0.0543	2.81	0.0484

Table 6S. Univariate Cox regression for baseline biomarkers. Continuous and ROC-based categorized biomarkers. Cut-offs and AUC values refer to ROC analysis for OS.

Abbreviations: cont., continuous; cat, categorical; AUC, area under the curve; ROC, receiver operating characteristic

Variable 1	Variable 2	Correlation	p-value
cox1	mtnd1	0.94	< 0.0001
TEMRA57	CD8	0.88	< 0.0001
CM28	CD4	0.89	< 0.0001
EMRA57	CD8	0.79	0.0001
cxcl10	SMI	0.67	0.0033
EM28	CM28	0.65	0.0035
TEMRA57	EMRA57	0.64	0.0039
timp1	mtnd1	0.65	0.0043
timp2	sRAGE	0.64	0.0055
CM28	EMRA28	0.61	0.0073
EM28	CD4	0.60	0.0080
timp1	cox1	0.59	0.0115
cxcl10	Muscle Area	0.55	0.0203
EM28	ccl4	0.54	0.0214
timp2	GDF15	0.54	0.0232
timp1	sRAGE	0.53	0.0250
mtnd1	dna	0.52	0.0284

Variable 1	Variable 2	Correlation	p-value
cox1	dna	0.50	0.0363
mtnd1	FGF21	0.50	0.0371
EMRA28	CD4	0.49	0.0388
TEMRA57	cxcl10	0.49	0.0412
EMRA28	CD8	0.48	0.0431
TEMRA57	Muscle Area	0.48	0.0443
TEMRA57	SMI	0.48	0.0453
timp1	ccl2	0.48	0.0478
treg	cxcl10	-0.47	0.0493

Table 7S. Significant correlation between circulating biomarkers, body composition and circulating immune-phenotype at baseline

Variable	Category	N	%
AJCC staging edition			
	3rd	2	0.3%
	4th	9	1.5%
	5th	27	4.5%
	6th	173	28.8%
	7th	234	39.0%
	Unknown	155	25.8%
Age at diagnosis	Mean $\pm$ SD	65.1 $\pm$ 10.2	
Ethnicity			
	Unknown	8	1.3%
	hispanic or latino	11	1.8%
	not hispanic or latino	449	74.8%
	not reported	132	22.0%
Sex			
	female	325	54.2%
	male	275	45.8%
Pathologic stage (AJCC)			
	Stage I	6	1.0%
	Stage IA	123	20.5%
	Stage IB	130	21.7%
	Stage II	1	0.2%
	Stage IIA	42	7.0%
	Stage IIB	57	9.5%
	Stage IIIA	63	10.5%

	Stage IIIB	10	1.7%
	Stage IV	23	3.8%
	Unknown	145	24.2%
Tobacco smoking status			
	Current Reformed Smoker for < or = 15 yrs	197	32.8%
	Current Reformed Smoker for > 15 yrs	163	27.2%
	Current Reformed Smoker, Duration Not Specified	4	0.7%
	Current Smoker	131	21.8%
	Lifelong Non-Smoker	85	14.2%
	Not Reported	18	3.0%
	Unknown	2	0.3%

Table 8S. Clinical characteristics of the TCGA-LUAD cohort (N = 600).

Biomarker	IMSIG Signature	Spearman ρ	p-value
AGER	B_cells	0.117	<0.01
AGER	Dendritic_cells	0.639	<0.001
AGER	Endothelial_cells	0.576	<0.001
AGER	Fibroblasts	-0.270	<0.001
AGER	Macrophages	0.356	<0.001
AGER	Monocytes	0.259	<0.001
AGER	NK_cells	0.305	<0.001
AGER	Neutrophils	0.511	<0.001
AGER	Proliferation	-0.516	<0.001
AGER	T_cells	0.126	<0.01
FGF21	B_cells	-0.082	<0.05
FGF21	Dendritic_cells	-0.267	<0.001
FGF21	Endothelial_cells	-0.176	<0.001
FGF21	Fibroblasts	0.002	0.95
FGF21	Macrophages	-0.201	<0.001
FGF21	Monocytes	-0.193	<0.001
FGF21	NK_cells	-0.088	<0.05
FGF21	Neutrophils	-0.189	<0.001
FGF21	Proliferation	0.271	<0.001
FGF21	T_cells	-0.110	<0.01
GDF15	B_cells	0.049	0.24
GDF15	Dendritic_cells	0.079	0.05
GDF15	Endothelial_cells	-0.021	0.61
GDF15	Fibroblasts	-0.081	<0.05
GDF15	Macrophages	-0.120	<0.01
GDF15	Monocytes	-0.144	<0.001
GDF15	NK_cells	-0.301	<0.001

Biomarker	IMSIG Signature	Spearman ρ	p-value
GDF15	Neutrophils	0.043	0.29
GDF15	Proliferation	-0.103	<0.05
GDF15	T_cells	-0.101	<0.05
PLIN2	B_cells	-0.132	<0.01
PLIN2	Dendritic_cells	0.189	<0.001
PLIN2	Endothelial_cells	0.173	<0.001
PLIN2	Fibroblasts	0.068	0.10
PLIN2	Macrophages	0.473	<0.001
PLIN2	Monocytes	0.475	<0.001
PLIN2	NK_cells	0.237	<0.001
PLIN2	Neutrophils	0.274	<0.001
PLIN2	Proliferation	0.200	<0.001
PLIN2	T_cells	0.072	0.08

Table 9S. Spearman correlation between gene expression of plasma biomarkers and immune microenvironment signatures (IMSIG) in lung adenocarcinomas from TCGA.

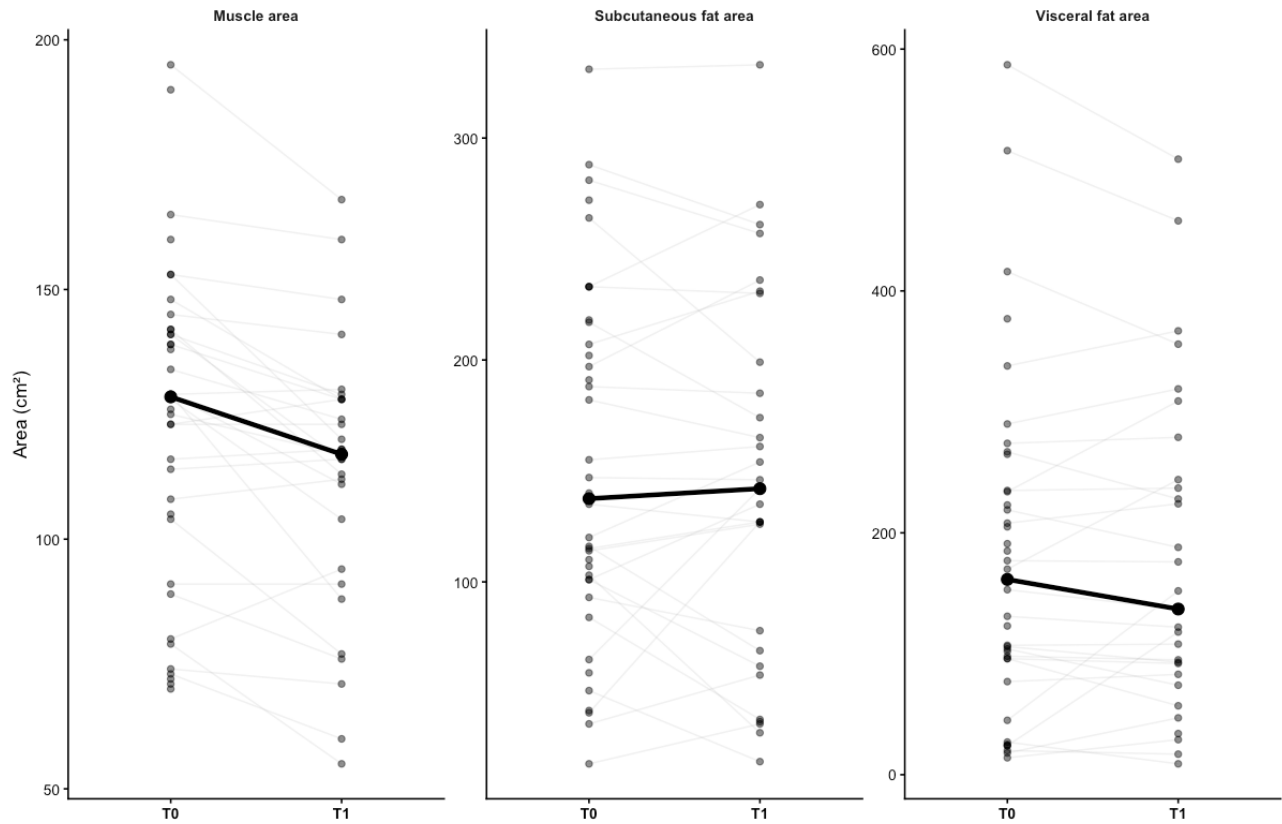


Figure 1S. Longitudinal changes in body composition parameters. Individual trajectories of muscle area, subcutaneous fat area, and visceral fat area from baseline (T0) to 3 months (T1) are shown. Thick black lines represent median values.

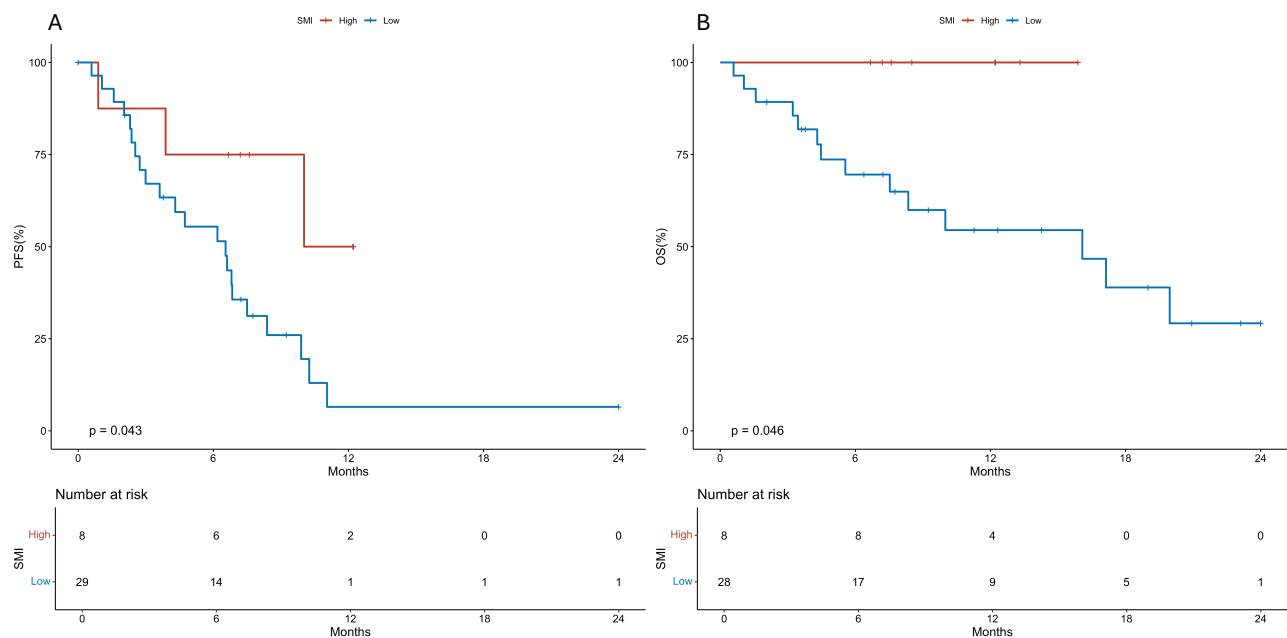


Figure 2S. Prognostic impact of skeletal muscle index (SMI) on survival outcomes. Kaplan–Meier curves for (A) progression-free survival (PFS) and (B) overall survival (OS) stratified by SMI status (low vs normal). Thresholds were defined based on established sex-specific cutoffs.

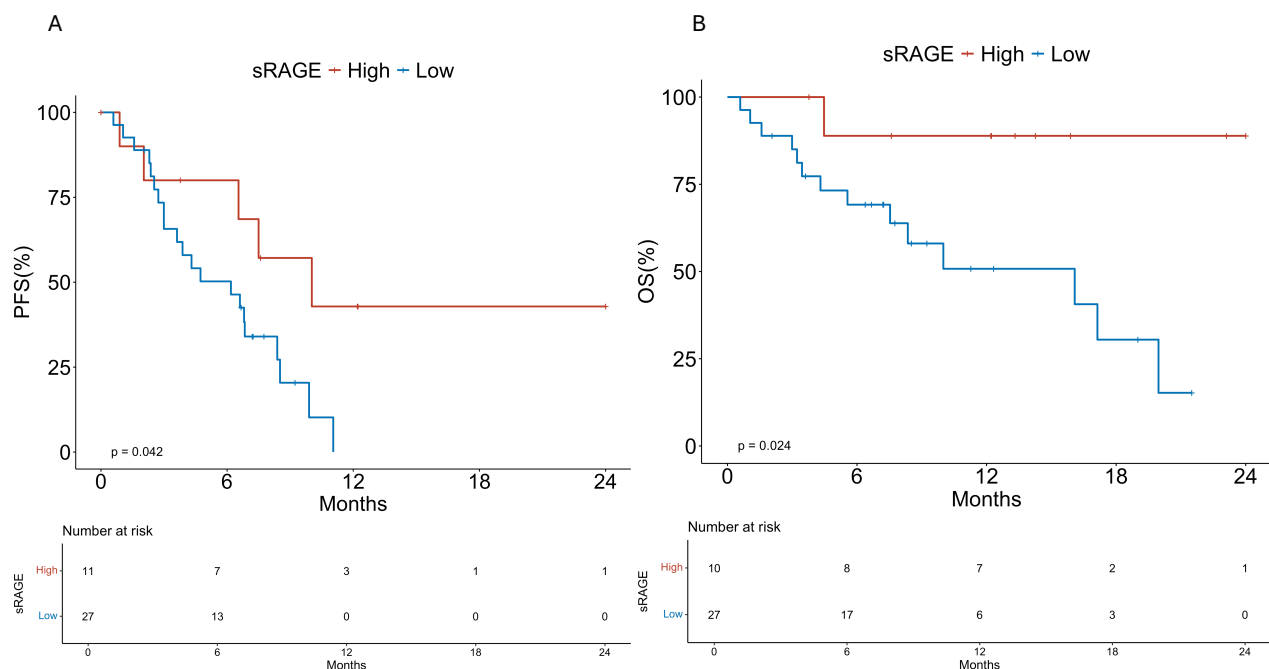
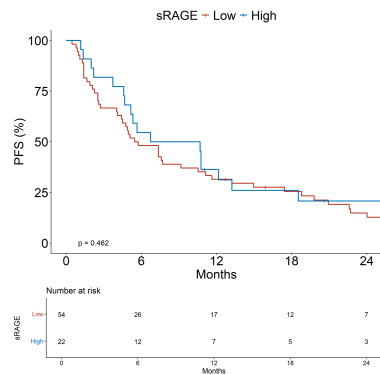
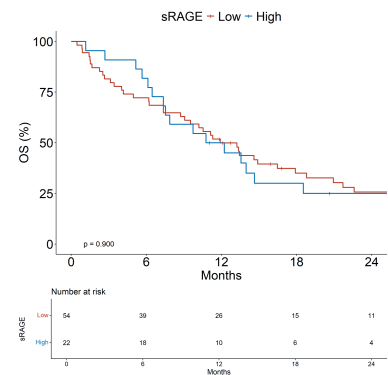


Figure 3S. Prognostic value of baseline plasma sRAGE levels in the SARC-LUNG Cohort. Kaplan–Meier curves for (A) progression-free survival (PFS) and (B) overall survival (OS) stratified by baseline sRAGE levels (high vs low), based on an ROC-derived optimal cutoff.

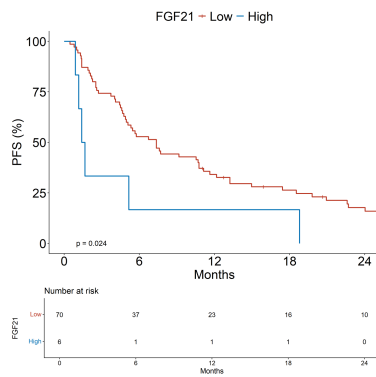
A



B



C



D

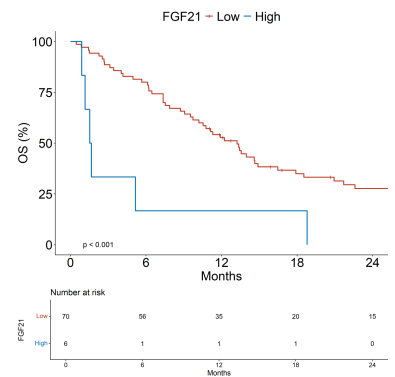


Figure 4S. Prognostic value of baseline plasma sRAGE and FGF21 levels in the Independent Cohort. Kaplan-Meier curves for progression-free survival (PFS) and overall survival (OS) stratified by baseline sRAGE (A-B) and FGF21 (C-D) levels (high vs low), based on standardized cutoffs. Number at risk is reported below each plot.