

Host-Derived Immunometabolic Biomarkers Identify Prognostic Profiles under Immunotherapy in Advanced NSCLC: the SARC-LUNG Study

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Abstract

Background

Immune checkpoint inhibitors (ICIs) improve outcomes in advanced non-small cell lung cancer (NSCLC), but predictive biomarkers remain limited. Host-derived immunometabolic factors may modulate response to ICIs.

Methods

In the prospective SARC-LUNG study, 40 patients with advanced NSCLC treated with first-line ICIs ($\pm$ chemotherapy) underwent longitudinal assessment of circulating biomarkers (sRAGE, FGF21, GDF15, cPLIN2), and CT-derived body composition parameters. Associations with progression-free survival (PFS), and overall survival (OS) were analyzed using Cox models. FGF21 and sRAGE were further assessed in an independent cohort of 76 patients. In silico transcriptomic analyses explored associations between biomarker-related genes and immune microenvironment signatures.

Results

High baseline sRAGE levels were associated with longer PFS and OS in the exploratory cohort, whereas increasing sRAGE levels during treatment correlated with response. Elevated FGF21 levels were associated with worse OS (HR 1.11, $p = 0.043$) and inversely correlated with lean mass. In the independent cohort, higher FGF21 levels remained independently associated with shorter PFS and OS, whereas sRAGE was not associated with survival. cPLIN2 and sRAGE gene expression were associated with immune-inflammatory phenotypes, while FGF21 and GDF15 with immune-desert phenotypes.

Conclusions

Host-derived immunometabolic biomarkers are associated with clinical outcomes and distinct immune microenvironment profiles in advanced NSCLC treated with ICIs.

Introduction

The introduction of immune checkpoint inhibitors (ICIs) has significantly improved outcomes in patients with advanced non-small cell lung cancer (NSCLC). Nevertheless, primary resistance remains common, and currently available biomarkers, such as tumor PD-L1 expression, only partially predict therapeutic benefit [1]. There is increasing recognition that other factors not directly derived from the tumor (hereafter referred to as “host-derived”), including systemic inflammation, metabolism and body composition, may influence the efficacy of ICIs [2–4].

Cancer cachexia, a multifactorial syndrome characterized by involuntary weight loss, muscle wasting, and metabolic dysregulation, affects up to 50% of patients with advanced solid tumors and is associated with impaired treatment tolerance and worse survival [5, 6]. In NSCLC, sarcopenia consistently emerges as a negative prognostic factor, even in patients with preserved body weight [7]. Recent evidence has also highlighted the so-called “obesity paradox”, whereby overweight and obese patients treated with ICIs often experience improved outcomes compared with their normal-weight counterparts [3, 8]. Altogether, these data suggest that systemic metabolic stress and body composition may shape not only prognosis but also sensitivity to immunotherapy. Circulating molecules involved in metabolism, body composition and immune regulation are therefore likely important in determining the efficacy of cancer treatment and patients’ outcome. Among them, Fibroblast Growth Factor 21 (FGF21), Growth Differentiation Factor 15 (GDF15), circulating Perilipin 2 (cPLIN2), and soluble Receptor for Advanced Glycation End-products (sRAGE) have been proposed as potential biomarkers of metabolic dysfunction, inflammation, catabolism, body composition and physical frailty [9–13]. Preclinical and translational studies indicate that these factors may modulate immune responses, tumor progression and outcomes through modulation of the tumor-immune interface or systemic homeostasis. The recent development of anti-GDF15 monoclonal antibodies, such as ponesimab and visugromab, further underscores the therapeutic and biomarker potential of this immunometabolic axis [14, 15].

Despite these insights, the prognostic and biological relevance of these biomarkers, in patients receiving ICIs remains poorly defined. To address this gap, we conducted the prospective SARC-LUNG study to investigate the prognostic impact of circulating immuno-metabolic biomarkers (sRAGE, FGF21, GDF15, cPLIN2) and body composition parameters in patients with advanced NSCLC treated with first-line immunotherapy. To assess the reproducibility of key signals, we subsequently evaluated the association of selected biomarkers with survival in an independent cohort of patients with comparable clinical characteristics. Finally, we explored the association between biomarker expression and immune-related signatures in lung cancer transcriptomic datasets to provide a broader biological context for our findings.

Materials and Methods

Study design

SARC-LUNG was a prospective, observational study conducted at the IRCCS Azienda Ospedaliero-Universitaria of Bologna, where a total of 40 patients with advanced NSCLC were enrolled. The study protocol was approved by the local ethics committee (570/2022/Oss/AOUBo) and all participants provided written informed consent. Eligible patients were adults (age ≥ 18 years) with histologically confirmed stage IIIB–IV NSCLC, candidate to first-line ICI, either as monotherapy or in combination with chemotherapy.

The primary objective of the study was to evaluate the prognostic relevance of circulating host-derived immunometabolic biomarkers in patients receiving ICIs. Plasma biomarkers (sRAGE, FGF21, cPLIN2,

GDF15) were selected a priori based on their established roles in systemic inflammation, senescence, metabolic stress, muscle/lipid regulation, and their emerging association with cancer progression and host vulnerability.

To explore the reproducibility of selected biomarker-outcome associations, an independent retrospective cohort of 76 patients with advanced NSCLC treated with first-line immunotherapy-based strategies at IRCCS Azienda Ospedaliera Metropolitana (Genoa, Italy) was used to validate the findings. Patients were selected based on clinical characteristics comparable to those of the SARC-LUNG cohort, including disease stage and treatment setting. Biomarker measurements and statistical analyses were conducted independently at the originating center according to predefined analytical criteria. The independent cohort study was approved by the Regional ethical committee (N. CET - Liguria: 191/2015 - DB id 2542).

Secondary aims included the assessment of their relationship with CT-derived body composition parameters and systemic inflammatory indices within the SARC-LUNG cohort. In addition, gene expression data from lung cancers included in The Cancer Genome Atlas (TCGA) were analyzed to investigate the association between biomarker expression and the immune composition of the tumor microenvironment.

Sample Collection

Peripheral blood samples were collected in EDTA tube at baseline (T0) and after three months of treatment (T1). Blood withdraw was performed in the morning after overnight fasting. Plasma was obtained from EDTA-treated blood by centrifugation at 1,000g for 15 minutes at room temperature and stored at -80°C until analysis. Plasma samples collected at baseline from the independent patient cohort (N = 76) were processed by two rounds of serial centrifugation (1,250 × g for 20 minutes, followed by 3,000 × g for 10 minutes) and subsequently stored at -80°C until use.

Body composition analysis

Body composition was assessed using computed tomography (CT) scans performed in routine clinical care at T0 and T1. A single axial slice at the level of the third lumbar vertebra (L3) was analyzed using semi-automated segmentation with 3D Slicer software to quantify skeletal muscle area (SMA), skeletal muscle index (SMI), subcutaneous fat area (SFA), and visceral fat area (VFA). SMI was normalized for patient height and sarcopenia was defined using previously validated sex-specific thresholds (Male: SMI < 53 cm²/m, Female: SMI < 41 cm²/m²) [16–18].

Haematochemical and inflammatory parameters

Baseline systemic inflammation was assessed using the derived neutrophil-to-lymphocyte ratio (dNLR), the platelet-to-lymphocyte ratio (PLR), and the Lung Immune Prognostic Index (LIPI), selected based on

their established prognostic value in NSCLC patients treated with ICIs [19–21]. dNLR was calculated as: absolute neutrophil count / (total white blood cell count – absolute neutrophil count), whereas the PLR was obtained as the ratio of absolute platelet count to absolute lymphocyte count. LIPI was defined using dNLR and lactate dehydrogenase (LDH) levels, according to established cut-offs [19].

Circulating plasma biomarkers evaluation

Plasma concentrations of GDF15, FGF21, and sRAGE were measured using the Simple Plex Human Cartridges (ProteinSimple/Bio-Techne) run on an Ella Automated Immunoassay System (ProteinSimple/Bio-Techne), according to manufacturer's instructions. Plasma cPLIN2 levels were quantified using the commercial Human ADRP (PLIN2) ELISA Kit (E-EL-H0278, ELabscience), according to the manufacturer's instructions. All samples were analyzed in duplicate and in batch to minimize inter-assay variability. Assay performance characteristics, including limits of detection and intra-/inter-assay coefficients of variation, were within the ranges specified by the manufacturers.

Outcome assessment

Clinical and pathological data were collected including age, sex, performance status, comorbidities, smoking history, histological subtype, molecular characterization, and treatment details. Tumor response was assessed radiologically according to RECIST 1.1 criteria [22]. Progression-free survival (PFS) was defined as the time from treatment initiation to radiological or clinical progression or death, and overall survival (OS) as the time from treatment initiation to death from any cause. Patients without an event were censored at the date of last follow-up. Median follow-up was estimated using the reverse Kaplan-Meier method. The objective response rate (ORR) was defined as the proportion of patients who achieved a complete or partial response among those evaluable for radiological assessment. Consequently, patients who achieved at least a partial response were considered as responders.

In Silico Transcriptomic Analysis

To complement and biologically contextualize the findings of the SARC-LUNG cohort, a transcriptomic analysis was conducted using RNA-sequencing data from primary lung adenocarcinoma (LUAD) samples available in TCGA. The analysis focused on four host-related genes, *AGER* (encoding for RAGE), *FGF21*, *GDF15*, and *PLIN2*, selected based on their association with systemic inflammation, body composition, and clinical outcomes in the prospective cohort. Raw HTSeq-Count data were retrieved from the Genomic Data Commons (GDC) using the TCGAbiolinks R package. After excluding technical replicates and duplicated entries, 600 unique tumor samples were retained for analysis. Gene expression data were normalized as log2 counts per million (logCPM) using the edgeR package. To estimate the cellular composition of the tumor microenvironment, Gene Set Variation Analysis (GSVA) was applied using the IMSIG signature, a validated immune and stromal deconvolution tool for bulk RNA-seq data [23]. IMSIG scores were computed for ten components: T cells, B cells, NK cells, Monocytes,

Macrophages, Dendritic cells, Neutrophils, Endothelial cells, Fibroblasts, and proliferation. Spearman rank correlation coefficients were calculated between gene expression levels of the four selected genes and each IMSIG-derived component. A p-value < 0.05 was considered statistically significant. Given the exploratory nature of these analyses, p-values were not adjusted for multiple comparisons.

Statistical Analysis

Continuous variables were reported as means ($\pm$ standard deviation) or medians with interquartile range according to distribution assessment and compared using paired t-tests or Wilcoxon signed-rank tests. Categorical variables were analyzed using chi-square or Fisher's exact tests. Kaplan-Meier estimates were used to calculate survival curves, and the log-rank test was employed for group comparisons. Univariate Cox regression models were applied to evaluate associations between clinical or biological variables and survival outcomes. Given the exploratory nature and limited sample size, multivariable analyses in the discovery cohort were restricted to avoid model overfitting. Plasma biomarkers were analyzed both as continuous variables (rescaled per 100 pg/mL to improve interpretability) and as categorical variables using ROC-derived thresholds for OS in the SARC-LUNG cohort. The corresponding area under the curve (AUC) values and cut-offs are reported in Supplementary Table S3.

In the independent cohort, standardized cut-offs derived as described above were applied for categorical analyses to minimize inter-center variability. Cox regression and log-rank tests were used for survival analyses accordingly. A p-value < 0.05 was considered statistically significant. All analyses were performed using R software, version 4.2.1 whereas data analysis for the validation cohort was conducted using Stata (Release 17; StataCorp LLC, College Station, TX, USA, 2021).

Results

Patients' Characteristics and Baseline Associations

The median age of the 40 SARC-LUNG patients enrolled was 70 years (range 49-83), and 67.5% (n=27/40) of participants were male (Table 1). Most patients had good performance status (ECOG 0–1, 87.5%, n=35/40) and non-squamous histology (82.5%, n=33/40). At baseline, 70% of patients received chemo-immunotherapy (n=28/40), while the remainder received ICI monotherapy (Table 1). Two patients did not receive any treatment due to fast clinical deterioration. Brain and liver metastases were observed in 27.5% (n=11/40) and 10% (n=4/40) of patients, respectively (Table 1).

Baseline analysis of body composition revealed that 72.5% of patients were sarcopenic (n=29/40), based on sex-specific skeletal muscle index (SMI) thresholds (Table 1). The median SMI was 43.4 cm²/m² (IQR 37.2-48.8), with a median muscle area of 128.5 cm² (IQR 104.2-141.8). Median visceral fat area (VFA) and subcutaneous fat area (SFA) were 161.5 cm² (IQR 96.0-234.8) and 137.5 cm² (IQR 101.0-214.5), respectively. Longitudinal changes in body composition parameters over the first 3 months were modest and highly heterogeneous, with no consistent directional pattern observed (Figure 1S)

Correlation analyses between circulating biomarkers (GDF15, FGF21, cPLIN2, sRAGE) at baseline (T0) and clinicopathological parameters reported no significant differences across clinical subgroups (Table 1S-4S). Notably, sRAGE levels were higher in patients aged ≥ 70 years (p-value < 0.001, Table 4S). Although no other significant difference in GDF15, FGF21, cPLIN2 or sRAGE plasma levels was observed across clinical subgroups, we noticed a trend in the levels of GDF15, cPLIN2, and sRAGE according to tumor expression of PD-L1. Specifically, GDF15 levels tend to be higher in patient with PD-L1 expression < 50%, while cPLIN2 and sRAGE levels tend to be lower (Table 1S-4S).

	SARC-LUNG Cohort (n=40)	Independent Cohort (n=76)	p value
Age			0.43
<70 years	18 (45.0%)	40 (52.6%)	
≥70 years	22 (55.0%)	36 (47.4%)	
Sex			0.82
female	13 (32.5%)	23 (30.2%)	
male	27 (67.5%)	53 (69.7%)	
ECOG PS			0.77
≥2	5 (12.5%)	8 (10.5%)	
0-1	35 (87.5%)	67 (88.1%)	
missing		1 (1.3%)	
Smoking history			0.14
current smoker	11 (27.5%)	34 (44.7%)	
former smoker	25 (62.5%)	35 (46.1%)	
never smoker	1 (2.5%)	4 (5.3%)	
missing	3 (7.5%)	3 (3.9%)	
BMI			
low	5 (12.5%)		
normal	18 (45.0%)		
over	17 (42.5%)		
missing		76 (100%)	
SMI			
high	9 (22.5%)		
low	29 (72.5%)		
missing	2 (5.0%)	76 (100%)	
Histology			0.81
nonsquamous	33 (82.5%)	64 (84.2%)	

	SARC-LUNG Cohort (n=40)	Independent Cohort (n=76)	p value
squamous	7 (17.5%)	12 (15,8%)	
Num. Metastatic Sites			0.18
>3	5 (12.5%)	13 (17.1%)	
0-3	35 (87.5%)	49 (63.4%)	
missing		8 (10.5%)	
PD-L1 expression			0.16
<50%	27 (67.5%)	45 (59.2%)	
≥50%	10 (25.0%)	29 (38.2%)	
not assessed	3 (7.5%)	2 (2.6%)	
KRAS			0.21
mutated	12 (30.0%)	27 (35.5%)	
wild type	28 (70.0%)	37 (48.7%)	
missing		12 (15.8%)	
Lung met.			
no	19 (47.5%)		
yes	21 (52.5%)		
missing		76 (100%)	
Brain met.			0.34
no	29 (72.5%)	56 (73.6%)	
yes	11 (27.5%)	14 (18.4%)	
Liver met.			0.52
no	36 (90.0%)	59 (77.6%)	
yes	4 (10.0%)	11 (14.5%)	
missing		6 (7.9%)	
Treatment			<0.001
CT-ICI	28 (70.0%)	28 (36.8%)	

	SARC-LUNG Cohort (n=40)	Independent Cohort (n=76)	p value
ICI	10 (25.0%)	48 (63.2%)	
Not treated	2 (5.0%)		

Table 1. Baseline characteristics

Abbreviations: Eastern Cooperative Oncology Group Performance Status, ECOG PS; BMI, body mass index; SMI, skeletal muscle index; CT, chemotherapy; ICI, immune-checkpoint inhibitor

Host-related biomarkers, body composition and inflammation

We next explored the possible association between biomarkers and anthropometric parameters. Correlation analyses revealed biologically consistent associations between biomarkers and body composition (Figure 1). cPLIN2 levels were positively correlated with VFA ($r = 0.57$, $p = 0.0006$) and SFA ($r = 0.55$, $p = 0.0012$) (Figure 1 and Table 2), consistent with its role as a proxy for body adiposity [10]. FGF21 showed an inverse correlation with both skeletal muscle area ($r = -0.35$, $p = 0.048$) and SMI ($r = -0.35$, $p < 0.048$) (Figure 1 and Table 2) in agreement with literature data [9,24]. Similarly, GDF15 tended toward a negative association with muscle indices, although these correlations did not reach statistical significance, whereas sRAGE levels were not associated with any body composition parameters (Table 5S). We then assessed correlations between biomarkers and benchmark inflammation-based prognostic scores. sRAGE levels were inversely correlated with both LIPI (LIPI; $r = -0.47$, $p\text{-value} = 0.0062$) and dNLR ($r = -0.39$, $p\text{-value} = 0.0297$) (Figure 1 and Table 2). sFGF21 correlated positively with PLR ($r = 0.43$, $p\text{-value} = 0.00138$), whereas cPLIN2 showed an inverse correlation with PLR ($r = -0.46$, $p\text{-value} < 0.0001$) and NLR (-0.35 , $p=0.0479$) (Figure 1 and Table 2). These findings indicate biologically consistent relationships between host-derived immuno-metabolic biomarkers, body composition, and systemic inflammation, supporting their potential role as integrative markers in patient assessment.

Heatmap showing pairwise Spearman correlation coefficients between baseline plasma biomarkers (GDF15, FGF21, cPLIN2, sRAGE), body composition parameters (skeletal muscle index, SMI, muscle area, visceral fat area, subcutaneous fat area), and inflammatory markers (NLR, dNLR, PLR, LDH, LIPI score). Positive correlations are depicted in red and negative in blue, with color intensity proportional to the strength of correlation.

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
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

Table 2. Significant correlation between circulating biomarkers, body composition, and inflammatory ratios at baseline (T0) within the SARC-LUNG Cohort.

Abbreviations: SMI, skeletal muscle index; NLR, neutrophil-to-lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; LIPI, lung-immune prognostic index; LDH, lactate dehydrogenase

Host-derived biomarkers and Clinical Outcomes

In the SARC-LUNG cohort, median OS was 17.1 months (95% CI, 10.0-not reached), and the median PFS was 6.8 months (95% CI, 4.3-10.0). The median time of follow up was 12.2 months (95% CI, 9.2-20.9).

The objective response rate (ORR) was 68.8% (95% CI, 0.50-0.83).

Baseline sarcopenia was associated with dismal clinical outcomes. Patients with low SMI at T0 experienced shorter PFS (6.1 vs 10.0 months, p-value < 0.05) and OS (16.1 months vs not reached, p-value = 0.046) (Figure 2S). Each unit decrease in SMI over the first three months of treatment was associated with a 30% increased risk of mortality (HR = 1.30, 95% CI 1.05-1.59; p-value = 0.012). Other body composition parameters, including BMI, subcutaneous or visceral fat area, were not associated with survival, neither at baseline nor measured dynamically over the first 3 months.

Regarding circulating biomarkers, patients with high baseline sRAGE levels (≥ 1065.5 pg/mL), dichotomized using a ROC-derived cut-off (Table 6S), had significantly longer PFS (10.0 vs 6.2 months, p-value = 0.042) and OS (not reached vs 16.1 months, p-value = 0.024) (Figure 3S). Notably, in univariate Cox regression, this association remained significant for PFS (HR = 0.35, 95% CI 0.12-0.99; p-value = 0.048), with a borderline association for OS (HR = 0.13, 95% CI 0.01 - 1.03 ; p-value = 0.054).

Among continuous biomarkers, higher baseline sFGF21 levels were the only circulating factor significantly associated with worse OS (HR = 1.11 per 100 pg/mL increase, 95% CI 1.00-1.22; p-value = 0.043) (Figure 2). No other significant associations with PFS or OS were found for baseline levels of GDF15, FGF21 (categorical), cPLIN2, or sRAGE (continuous). A full summary of survival analyses is provided in Table 6S.

Among the 27 patients with matched blood at T0 and T1 time points, sRAGE increased significantly in responders compared to non-responders from baseline to week 12 (median Δ sRAGE: +486 vs -71.5 pg/mL; p-value = 0.012) (Figure 3). No other significant variations in the levels of host-related circulating biomarkers were observed in relation to treatment response (Figure 3).

Independent retrospective cohort analysis

An independent cohort of 76 patients with advanced NSCLC treated with first-line ICI-based therapy was analyzed to validate the prognostic significance of two biomarkers that exhibited a signal in the exploratory cohort, such as FGF21, sRAGE. The independent cohort exhibited clinical characteristics comparable to those of the primary cohort; most patients were male (69.7%, n= 53/76), with a median age of 69 years (IQR 59-73). Most patients had good ECOG PS (0–1, 88.2%, n=67/76) and non-squamous histology (84.3%, n=64/76). 63.2% of patients received upfront chemo-immunotherapy, while 36.8% were treated with pembrolizumab monotherapy. Brain and liver metastases were present in 18.4% and 14.5% of patients, respectively (Table 1).

In Cox regression models using baseline values as continuous variables (per 100 pg/mL increase), higher FGF21 levels were significantly associated with worse outcomes, confirming the previous data from the exploratory cohort.

In the fully adjusted model (sex, age, histology, treatment type, number of metastatic sites, ECOG PS), FGF21 levels remained independently associated with increased mortality (OS: HR 1.23, 95% CI 1.09-

1.38; p-value =0.001) and progression risk (PFS: HR 1.15, 95% CI 1.03-1.27; p-value =0.012) (Figure 2).

Applying a standardized cut-off, high baseline FGF21 levels were significantly associated with shorter OS (Figure 2B). Notably, in the fully adjusted model, elevated FGF21 was independently associated with markedly increased mortality risk (OS: HR 16.26, 95% CI 2.80-94.29; p-value=0.002) and shorter PFS (HR =7.53, 95% CI 1.80-31.48; p-value=0.006). On the contrary, categorical sRAGE levels were not associated with OS or PFS in either univariate or multivariable analyses (Figure 4S).

Correlation between immune-related transcriptional signature and host-derived biomarkers

A total of 600 LUAD tumor samples from the TCGA cohort were included in the transcriptomic analysis. Clinical characteristics of the cohort are summarized in Table 7S.

Expression levels of *AGER*, *FGF21*, *GDF15*, and *PLIN2* were correlated with immune and stromal components of the tumor microenvironment, as inferred by the IMSIG deconvolution signature (Figure 4).

AGER expression showed strong positive correlations with dendritic cells ($r = 0.639$, $p < 0.001$), endothelial cells ($r = 0.576$, $p\text{-value} < 0.001$), macrophages ($r = 0.356$, $p\text{-value} < 0.001$), NK cells ($r = 0.305$, $p\text{-value} < 0.001$), and neutrophils ($r = 0.511$, $p\text{-value} < 0.001$) (Figure 4 and Table 8S). A moderate inverse correlation was observed with the proliferation signature ($r = -0.516$, $p\text{-value} < 0.001$) (Figure 4), suggesting that high *AGER* expression is associated with a tumor microenvironment enriched in immune cells and a less proliferative tumor.

FGF21 expression was negatively associated with multiple immune populations, including dendritic cells ($r = -0.267$, $p < 0.001$), macrophages ($r = -0.201$, $p < 0.001$) and monocytes ($r = -0.193$, $p < 0.001$) (Figure 4 and Table 8S), while showing a weak positive correlation with the proliferation signature ($r = 0.271$, $p < 0.001$), consistent with an immune-deserted, proliferative phenotype.

GDF15 expression showed relatively weak correlations overall, with the strongest negative associations with NK cells ($r = -0.301$, $p < 0.001$), monocytes ($r = -0.144$, $p < 0.001$), and fibroblasts ($r = -0.081$, $p < 0.05$) (Table 8S).

PLIN2 expression was positively correlated with macrophages ($r = 0.473$, $p < 0.001$), monocytes ($r = 0.475$, $p < 0.001$), and neutrophils ($r = 0.274$, $p < 0.001$), while displayed weaker or non-significant correlations with lymphoid components (Figure 4 and Table 8S).

These findings suggest that host-derived immunometabolic biomarkers show distinct associations with the immune landscape of LUAD tumors, with *AGER* and *PLIN2* linked to immune-inflammatory phenotypes whereas *FGF21* and *GDF15* associated with relatively immune-deprived profiles.

Discussion

In this prospective study of patients with advanced NSCLC receiving first-line ICI-based strategies, we investigated the prognostic role of host-related circulating biomarkers, CT-derived body composition parameters, and circulating inflammatory markers. Our integrative approach revealed that a combination of metabolic, inflammatory, and immunologic parameters may influence outcomes beyond traditional tumor-centric metrics. Remarkably, the consistency of selected biomarker-outcome associations was further explored in an independent external cohort of NSCLC patients, supporting the robustness and reproducibility of our findings.

Among the evaluated biomarkers, FGF21, a stress-induced mitokine implicated in metabolic dysfunction and cachexia [9], emerged as a consistent adverse prognostic marker. In the prospective SARC-LUNG cohort, higher baseline FGF21 levels were associated with shorter OS, and interestingly this association was consistently confirmed in the independent patient cohort, where FGF21 remained independently linked to both OS and PFS after adjustment for major clinical covariates. The direction and magnitude of the effect were concordant across continuous and standardized categorical analyses, supporting the reproducibility of this prognostic marker. FGF21 also inversely correlated with skeletal muscle mass and positively with PLR suggesting that FGF21 may have a detrimental immuno-metabolic role. In addition, the substantial inverse correlation between infiltrating IMSIG signatures and the proliferation index, coupled with findings from the prospective cohort, supports prior research suggesting that elevated FGF21 may indicate systemic stress and immune suppression [26,27]. These observations are aligned with emerging evidence from other solid tumors, where high circulating FGF21 has been associated with unfavorable outcomes or more advanced disease stages [27-29], reinforcing the role of FGF21 as a systemic stress mediator at the interface between metabolism and lung cancer progression [25,30].

In the exploratory SARC-LUNG cohort, sRAGE emerged as a potentially protective biomarker under immunotherapy. However, this signal was not confirmed in the independent cohort, suggesting that baseline sRAGE levels may not represent a consistently reproducible prognostic biomarker. In the exploratory cohort, high baseline sRAGE levels were associated with improved PFS and OS, while an increase in sRAGE from T0 to T1 was significantly associated with treatment response. These findings are consistent with previous reports linking lower circulating sRAGE levels to advanced disease and worse prognosis in NSCLC [12,31], and with the biological role of sRAGE as a soluble decoy receptor capable of buffering RAGE-mediated proinflammatory signaling [32]. Although RAGE is highly expressed in alveolar type I epithelial cells, its expression is markedly reduced in NSCLC, and its restoration in preclinical models suppresses tumor progression [33]. Circulating sRAGE has thus been proposed as a surrogate marker of pulmonary epithelial integrity and immune-metabolic resilience [34,35]. In our study, its inverse correlations with LIPI and dNLR further support its association with a lower systemic inflammatory burden. Transcriptomic analysis further revealed a positive correlation between *AGER* (encoding for RAGE) expression and immune-signatures, reinforcing the biological relevance of this axis in the tumor microenvironment.

Circulating levels of GDF15, another mitokine frequently elevated in cancer-related cachexia [11,14], were not significantly associated with survival in the exploratory cohort, in contrast with previous reports [11]. Differences in cohort characteristics (e.g., age and/or tumor GDF15 expression) may explain these discrepancies. Nonetheless, a trend toward an inverse correlation with muscle mass was observed, supporting its link with sarcopenia [11]. This suggests that circulating GDF15 levels, while helpful in revealing actual state of sarcopenia, may not be as effective in predicting PFS and OS, at variance with intra-tumoral GDF15 expression [36]. Transcriptomic data also revealed that tumors with high *GDF15* expression exhibited immune-desert phenotypes, consistent with its role in immune evasion through dendritic cell suppression and Treg activation [37,38] which can be related with the prognostic relevance under immunotherapy in NSCLC [11,14,39]. These observations reflect the findings from the phase II NIPICOL trial in metastatic colorectal cancer, where high GDF15 predicted worse outcomes only in sarcopenic patients treated with ICIs [40], suggesting a clinically relevant synergy between metabolic inflammation and muscle depletion.

In terms of body composition, baseline sarcopenia and loss of skeletal muscle during treatment (Δ SMI) were independently associated with worse survival outcomes, confirming previous studies and reinforcing the prognostic value of longitudinal CT-based metrics [16-18]. While sarcopenia was clearly detrimental, we did not observe a direct protective effect of adiposity. However, our data may provide a mechanistic interpretation of the so-called obesity paradox described in multiple ICI-treated cohorts [3,8]. Specifically, the soluble form of PLIN2 (sPLIN2), a protein usually associated to intracellular lipid droplets, was positively correlated with both subcutaneous and visceral fat area in our cohort, confirming previous data [10]. While the prognostic significance of PLIN2 varies across cancer types, recent meta-analytic data indicate an overall trend toward unfavorable outcomes in solid tumors with high PLIN2 expression [41], although its impact under ICIs remains undefined. Remarkably, transcriptomic analysis in TCGA cohort revealed that tumors with elevated PLIN2 expression were associated with high proliferation but also enriched for immune-inflamed signatures. These data suggest that lipid metabolic features may be associated with biological aggressiveness but also favor tumor immunogenicity. These findings align with the recent pan-cancer study by Alden et al., which demonstrated that obesity, defined by BMI, was associated with improved outcomes to ICI therapy, particularly in tumors with high immune infiltration and IFN- γ signaling [8]. Our results extend this concept by linking adiposity-associated biomarkers, such as sPLIN2, to a favorable tumor immune contexture.

Consistently, patients with tumors expressing PD-L1 $\geq 50\%$ appeared to display a distinct baseline biological profile, as suggested by the distribution of sPLIN2, GDF15 and sRAGE levels. Although these differences did not reach statistical significance, likely due to the limited sample size, they showed a coherent trend suggesting that patients with higher PD-L1 expression may present a more favorable systemic profile, characterized by lower GDF15 and higher cPLIN2 and sRAGE levels compared to those with PD-L1 $< 50\%$. These observations raise the hypothesis that tumor PD-L1 expression may be linked to broader host-related features, including body composition and systemic inflammation. This hypothesis and the possible causality direction need further investigations to be confirmed.

This study has several limitations. First, the SARC-LUNG cohort is monocentric and relatively small, which reduces statistical power and may limit the generalizability of some exploratory findings, particularly for biomarkers with modest effect sizes. Although we partially mitigated this limitation by evaluating FGF21 and sRAGE in an independent external cohort and by leveraging a large TCGA dataset, heterogeneity in patient selection, treatment regimens and biomarker assays between centers cannot be excluded. Second, the number of events in the independent cohort was limited, raising the possibility of overfitting in multivariable Cox models and contributing to the wide confidence intervals observed for categorical FGF21 analyses. Third, no formal correction for multiple testing was applied in either the clinical or transcriptomic analyses, which were conceived as hypothesis-generating. Therefore, our results should be interpreted with appropriate caution and confirmed in larger, dedicated studies. Finally, potential residual confounding by unmeasured variables, including comorbidities and concomitant medications, cannot be ruled out.

Despite these limitations, the prospective design, the use of standardized biomarker measurements, and the consistency observed across clinical, radiological, immunologic, and transcriptomic data support the validity of our findings.

Rather than identifying a single predictive biomarker, our findings support a broader immunometabolic framework in which host-related factors, including systemic inflammation, body composition, and circulating metabolic mediators, synergistically contribute to shaping response to immunotherapy. In this context, FGF21 may represent a robust marker of adverse systemic conditions, while other biomarkers such as sRAGE may reflect dynamic host responses during treatment.

These findings encourage further exploration of immune-metabolic crosstalk and support the integration of host biology into future predictive models for immunotherapy.

Declarations

Ethics approval and consent to participate

The protocol was approved by the local ethics committee (Comitato Etico di Area Vasta Emilia Centro, n. 570/2022/Oss/AOUBo; Comitato etico territoriale Regione Liguria n. 191/2015 - DB id 2542) and all participants provided written informed consent.

Consent for publication

Not applicable.

Availability of data and material

The data underlying this article cannot be shared due to the privacy of individuals who participated in the study, as stated by the local Ethics Committee (approval no. 570/2022/Oss/AOUBo, no. PR

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Author contributions

Andrea De Giglio, MD, PhD (Conceptualization; Data curation; Formal Analysis; Investigation; Methodology; Visualization; Writing-original draft; Writing-review and editing), Maria Conte, BS, PhD (Data curation; Investigation; Formal Analysis; Visualization; Writing-original draft; Writing-review and editing), Francesco Galuppi, MD (Data curation; Formal Analysis; Writing-review and editing), Francesca Lo Bianco, MD (Data curation; Writing-review and editing), Ilaria Ricciotti, MD (Data curation; Writing-review and editing), Alessandro Di Federico, MD, (Writing-review and editing), Valentina Favorito, MD, (Data Curation; Writing-review and editing), Lorenzo Trofarello, BS (Data curation; Writing-review and editing), Francesco Mantuano, MD (Writing-review and editing), Francesca Sperandi, MD (Writing-review and editing), Francesco Gelsomino, MD, PhD (Writing-review and editing), Stefano Brocchi, MD, (Data curation, Writing-review and editing), Cristina Mosconi, MD (Supervision; Validation; Writing-review and editing), Stefano Salvioli, BS, PhD (Conceptualization; Formal Analysis; Supervision; Funding; Validation; Writing-review and editing), Andrea Ardizzoni, MD, (Conceptualization; Project administration; Supervision; Validation; Writing-review and editing), Simona Coco, PhD (Data curation, Investigation;

Methodology; Writing-review and editing), Sara Santamaria, PhD (Data curation, Investigation; Methodology; Writing-review and editing), Alessandra Rosa, PhD (Formal Analysis; Writing-review and editing), Carlo Genova, MD, PhD (Writing-review and editing).

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Competing interests

MC, SC, FG, SS, AR, FLB, MN, IR, VF, LT, FM, FS, SB, CM, CG, SS declare no potential conflicts of interests.

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Figures

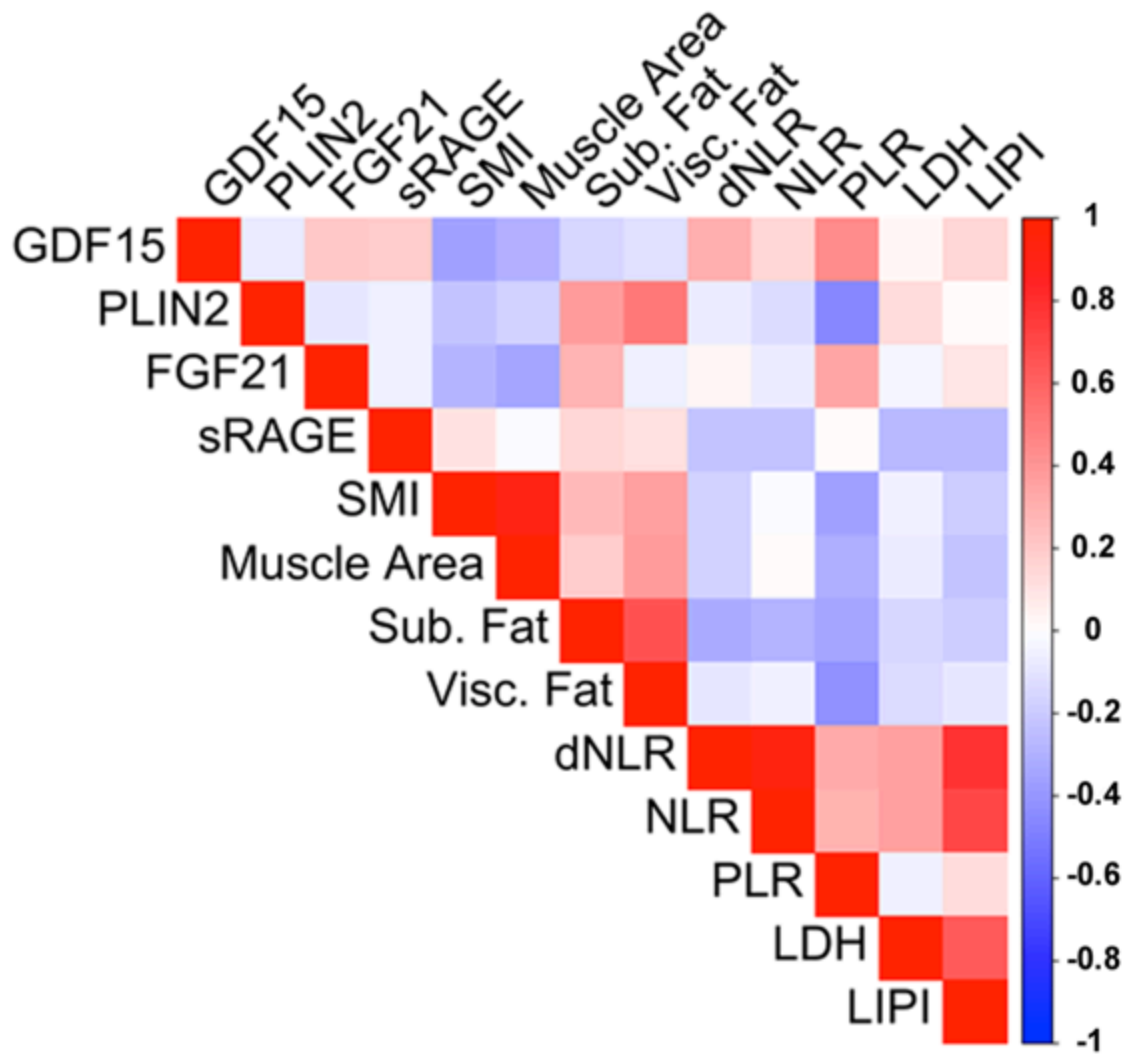


Figure 1

Correlation matrix between circulating biomarkers, body composition metrics, and systemic inflammation indices.

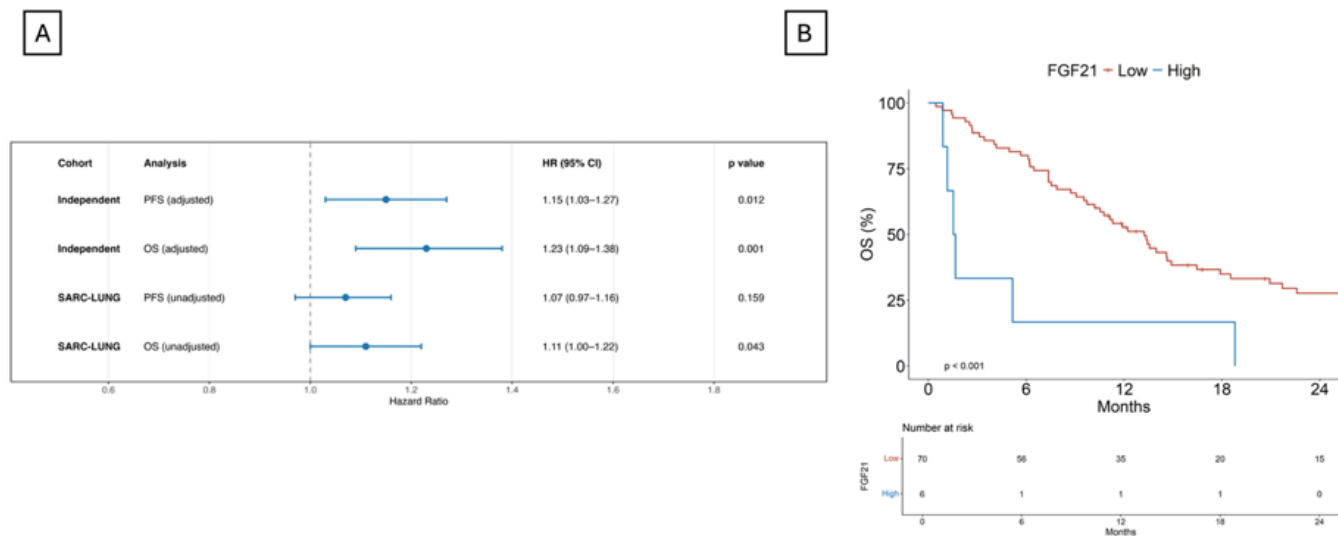


Figure 2

Prognostic impact of baseline FGF21 in advanced NSCLC treated with first-line ICI-based therapy. (A) Forest plot of continuous FGF21 models (per 100 pg/mL increase) across the SARC-LUNG and independent cohorts. In the exploratory SARC-LUNG cohort, estimates were derived from univariate Cox models, whereas in the independent cohort hazard ratios were obtained from multivariable models adjusted for major clinical covariates. (B) Kaplan–Meier overall survival curves according to baseline FGF21 categories (high vs low) in the independent cohort.

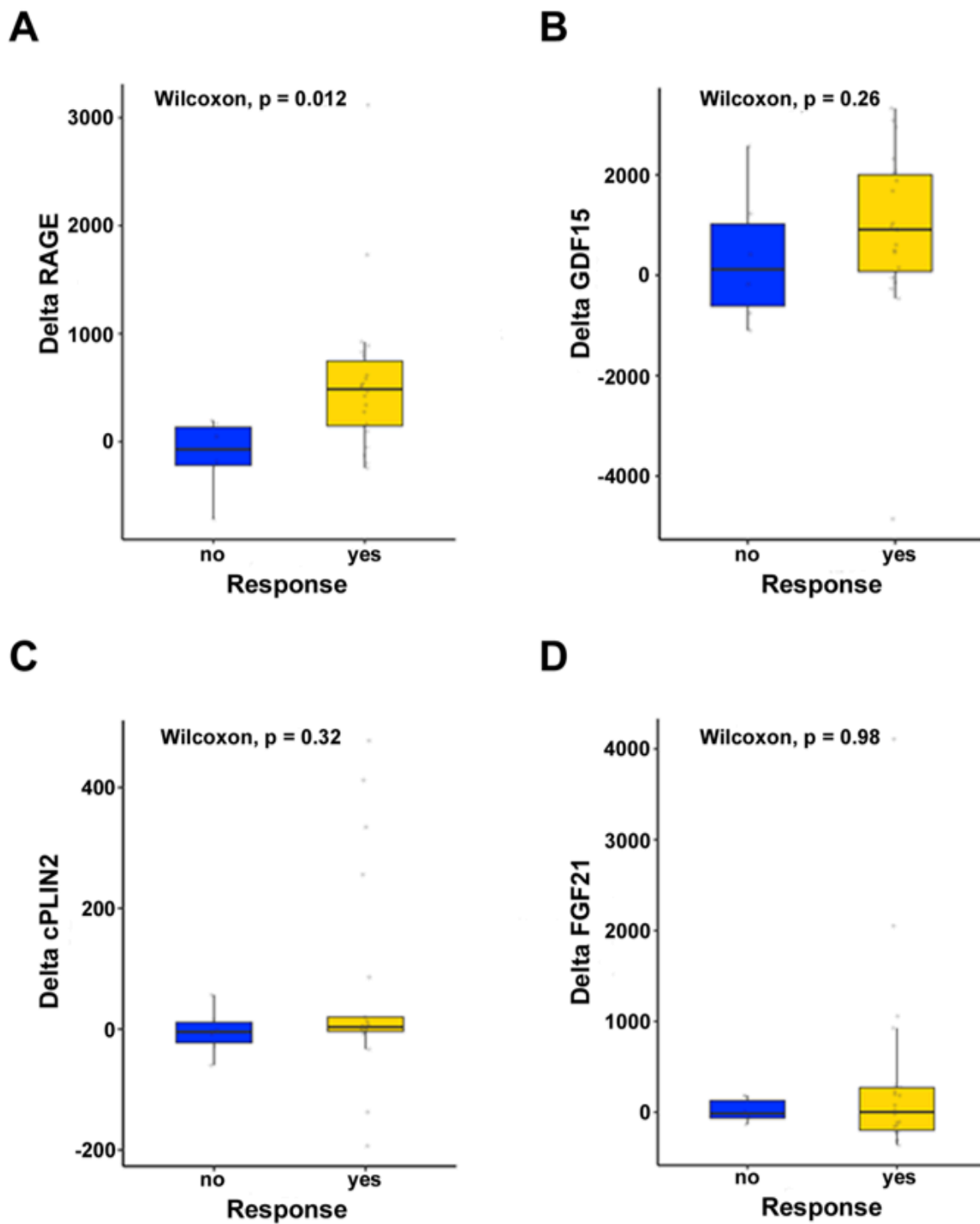


Figure 3

Association of plasma biomarkers with early treatment response.

Boxplots showing plasma concentrations variation between T0 to T1 of (A) sRAGE, (B) GDF15, (C) cPLIN2, and (D) FGF21 in responders vs non-responders to immunotherapy-based treatment.

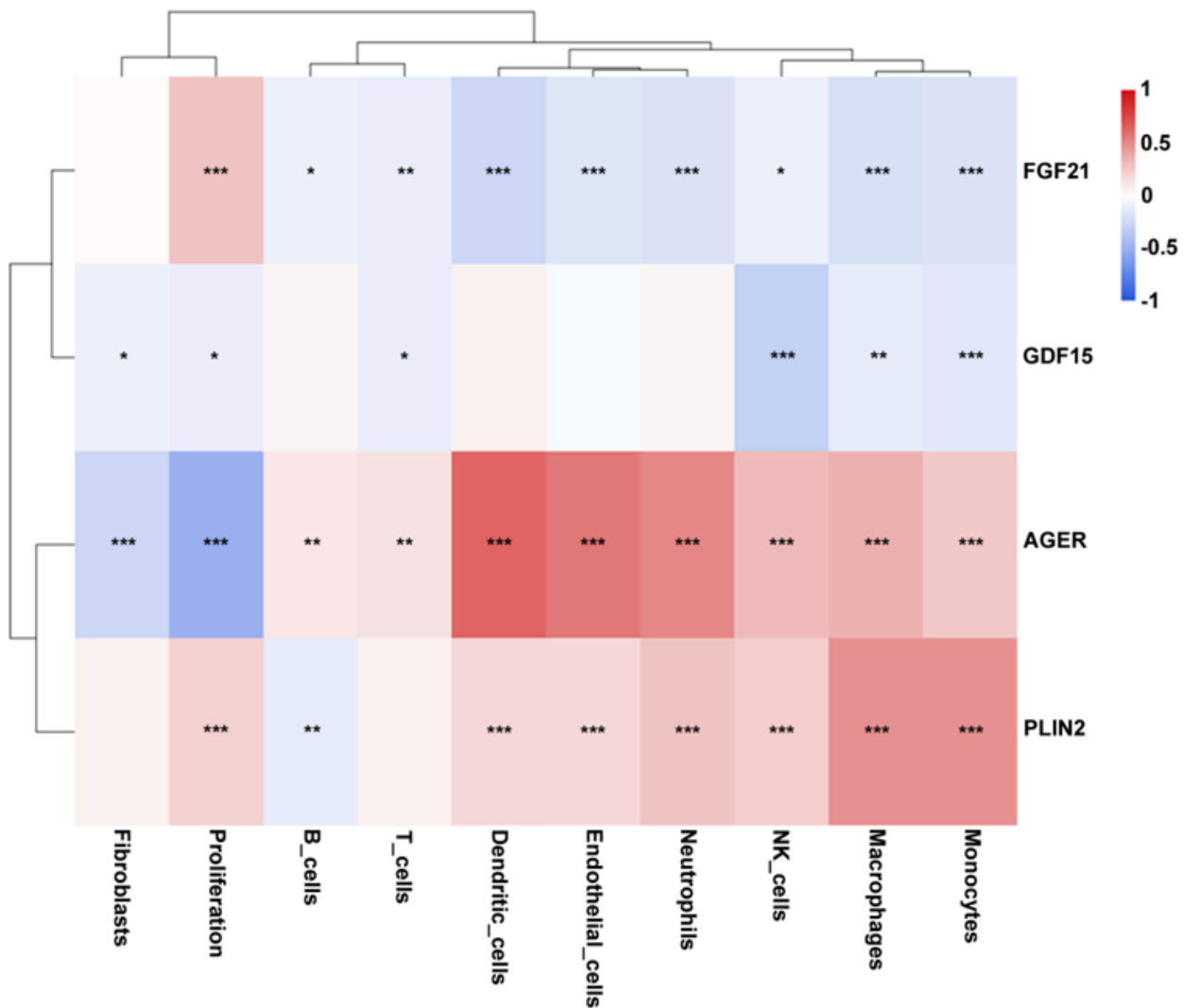


Figure 4

Correlation between immune-related transcriptional signatures and expression of biomarker genes. Heatmap depicting the correlation between tumor mRNA expression levels of AGER, GDF15, PLIN2, and RAGE and IMSIG-defined immune cell signatures from TCGA lung adenocarcinoma datasets. Spearman correlation coefficients are color-coded; asterisks indicate significant associations (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

Supplementary Files

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