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PROGNOSTIC VALUE OF IFNγ-ASSOCIATED GENES SIGNATURE IN LUNG SQUAMOUS CELL CARCINOMA: TCGA-BASED ANALYSIS

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Abstract. Lung squamous cell carcinoma (LUSC) represents the second most prevalent histological subtype of non-small cell lung cancer and is characterized by a high level of genomic instability, elevated mutational burden, and marked immune infiltration. These features underscore the potential of immunotherapy in this context; however, clinical responses remain heterogeneous. One of the promising molecular biomarkers of immune activation is the IFNγ-associated gene signature, which comprises the expression of ten transcriptomic markers involved in the interferon-gamma (IFNγ) signaling cascade: IDO1, IRF9, CCR5, STAT1, CXCL9, CXCL10, CXCL11, PRF1, IFNG, and HLA-DRA. The objective of this study was to evaluate the association between the expression level of the IFNγ gene signature and clinicopathological as well as molecular characteristics in patients with squamous cell carcinoma of the lung, using open-access data from the TCGA-LUSC cohort. The analysis included 419 patients with complete clinical, pathological, transcriptomic, survival, and mutation data (TP53, TTN, PIK3CA, KEAP1/NFE2L2). The IFNγ signature score was calculated as the mean $\log_2$(RSEM+1) of ten genes. ROC analysis set a threshold at 7.32, stratifying patients into low (n=196) and high (n=223) expression groups. Statistical analysis in Stata 19.5 included χ^2 tests for categorical variables, Spearman's correlation (visualized as a heatmap), Kaplan–Meier survival curves with log-rank testing, and multivariate Cox regression (HRs, 95 % CIs, p-values). Significance was set at $p<0.05$.

Correlation analysis revealed a high degree of concordance in expression across most genes within the signature, particularly for IDO1 ($\rho=0.74$), as well as CXCL9, CXCL10, and CXCL11 (all $\rho\approx0.40$), suggesting common transcriptional regulation mechanisms. In the demographic analysis, the mean age was 67.0±8.53 years, with no significant differences between expression groups ($p=0.930$); similarly, sex ($p=0.750$) and disease stage ($p=0.503$) were not associated with the level of IFNγ signature expression. Mutation analysis indicated that TTN, TP53, and PIK3CA mutations were not significantly associated with IFNγ signature expression levels ($p>0.05$); however, KEAP1/NFE2L2 mutations were more frequently observed in patients with high expression of the signature (35.9 % vs. 18.9 %, $p<0.0001$). Kaplan–Meier analysis showed a median overall survival of 55.2 months in the high-expression group versus 44.8 months in the low-expression group; however, the log-rank test did not reveal a statistically significant difference ($\chi^2(1)=0.37$, $p=0.5453$). In the Cox regression model, the IFNγ signature was not independently associated with survival (HR=0.94; 95 % CI: 0.70–1.28; $p=0.711$), unlike TP53 (HR=0.53; $p=0.009$) and TTN mutations (HR=0.58; $p=0.005$), which were associated with reduced mortality risk.

In conclusion, the results demonstrate a high transcriptional concordance among genes within the IFNγ signature and its association with certain molecular characteristics; however, the signature does not appear to possess independent prognostic value in patients with lung squamous cell carcinoma.

Keywords: IFNγ-associated gene signature, lung squamous cell carcinoma, immunotherapy, prognosis, biomarker.

Introduction. Lung squamous cell carcinoma (LUSC) is the second most common histological subtype of non-small cell lung cancer, characterized by an aggressive clinical course, a high degree of genomic instability, and a limited spectrum of actionable therapeutic targets [1, 2]. Given the high mutational burden and frequent immune infiltration of tumors, patients with LUSC represent a critical subgroup for evaluating the effectiveness of immunotherapy, particularly immune checkpoint inhibitors (ICIs) [3, 4].

However, the response to immunotherapy is highly variable, highlighting the urgent need for accurate biomarkers of immune activity [5, 6]. One promising candidate is the IFNγ-associated gene signature, which reflects the expression of genes transcriptionally activated in response to interferon gamma (IFNγ), a key Th1-type cytokine with potent antitumor properties [7, 8].

The aim of the study. The genes constituting the IFNγ signature (including CXCL9, CXCL10, CXCL11, IDO1, IRF9, CCR5, STAT1, PRF1, IFNG, and HLA-DRA) are involved in immune cell chemotaxis, T lymphocyte activation, antigen presentation, and tumor cell elimination [9, 10]. Previous studies have shown that high expression of this gene signature is associated with favorable prognosis and enhanced responsiveness to ICIs in various malignancies, including lung adenocarcinoma [11, 12].

Nonetheless, the role of the IFNγ signature in LUSC remains poorly understood. In particular, it is unclear to what extent its expression correlates with key somatic mutations (e.g., TTN, TP53, PIK3CA, and KEAP1/NFE2L2), tumor immune microenvironment characteristics, and overall patient survival [13, 14].

We hypothesize that the IFNγ-associated gene signature may serve as a potential marker of immune activation linked to mutational status and clinical outcomes in patients with LUSC. Therefore, the objective of this research was to analyze the association between the expression of the IFNγ-associated gene signature and clinicomolecular characteristics, as well as to evaluate its prognostic

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significance in patients with lung squamous cell carcinoma based on TCGA data.

Materials and methods.

Data Collection

For this study, clinical and molecular genetic data were obtained from three public cancer genomics repositories: UCSC Xena Browser (https://xenabrowser.net), cBioPortal (https://www.cbioportal.org/), and The Cancer Genome Atlas (TCGA, https://portal.gdc.cancer.gov/). The study cohort consisted of patients diagnosed with lung squamous cell carcinoma (LUSC) and enrolled in the TCGA-LUSC project (n=504). A final dataset of 419 patients was selected based on the availability of complete clinical and molecular information. Inclusion criteria encompassed documented survival status and duration, patient age, tumor stage, sex, mutation status for TP53, TTN, PIK3CA, and KEAP1/NFE2L2, as well as transcriptomic data for the following genes: CXCL9, CXCL10, CXCL11, IDO1, IRF9, CCR5, STAT1, PRF1, IFNG, and HLA-DRA (Fig. 1).

The study was approved by the Bioethics Committee for Experimental and Clinical Research of the Educational and Scientific Medical Institute of Sumy State University (Protocol No. 3/12, December 17, 2024). As the medical data used were publicly available and analyzed retrospectively, written informed consent was not required.

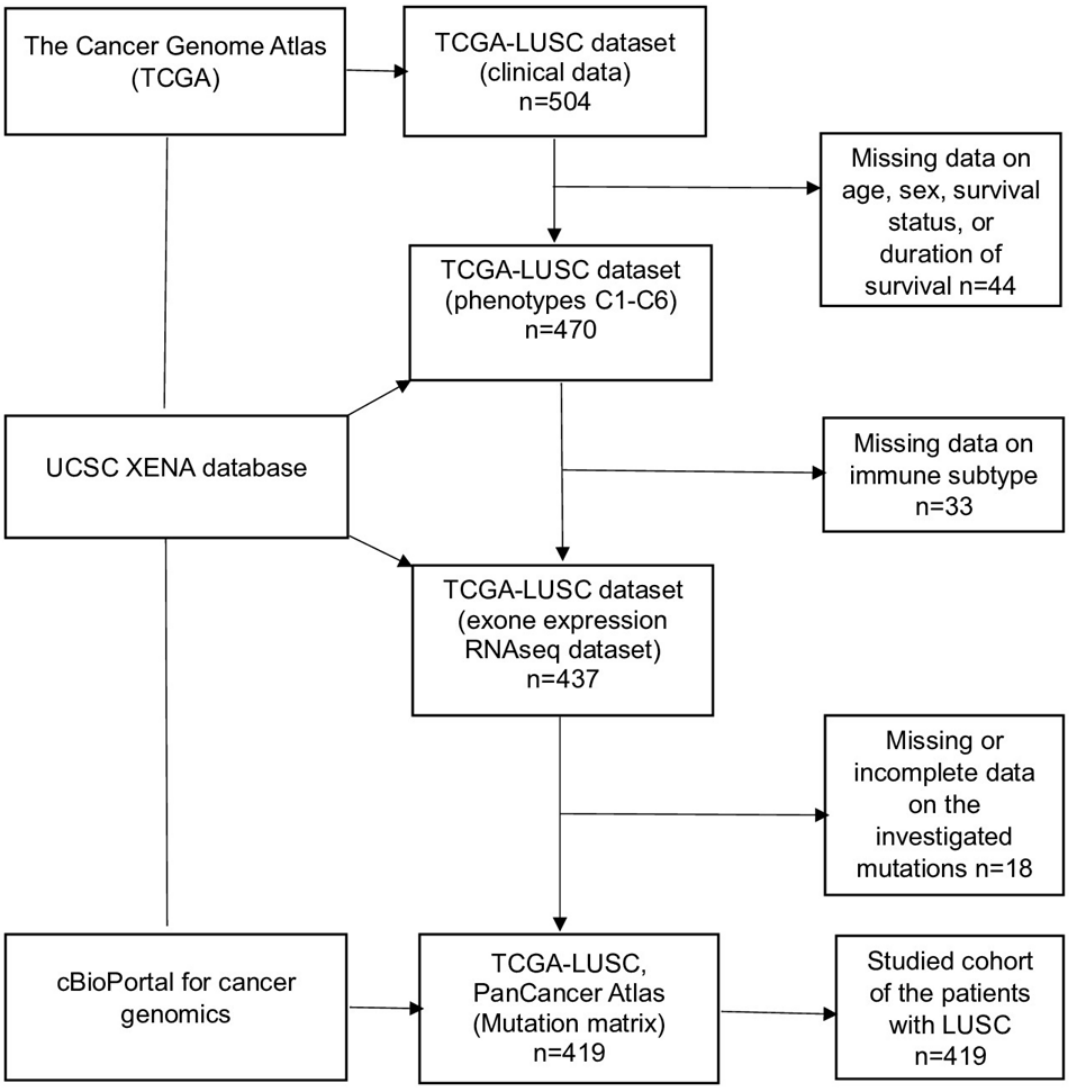

Fig. 1. Flowchart illustrating the selection of patients with lung squamous cell carcinoma from public cancer repositories for inclusion in the study

Evaluation of IFNγ-associated gene signature expression

To quantify the expression of the IFNγ-associated gene signature, transcriptomic expression data for ten genes involved in IFNγ-mediated immune responses – IDO1, IRF9, CCR5, STAT1, CXCL9, CXCL10, CXCL11, PRF1, IFNG, and HLA-DRA [7] – were downloaded from the UCSC Xena Browser repository. The gene expression values were provided as normalized transcriptomic levels ($\log_2$(RSEM+1)) and required no additional processing. The expression score of the IFNγ-associated gene signature was calculated for each sample as the arithmetic mean of the log-transformed expression values of the aforementioned genes. Based on the results of receiver operating characteristic (ROC) analysis, a threshold value of 7.32

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log_2(RSEM+1) was established to stratify patients into low (<7.32) and high (≥7.32) expression groups.

Statistical analysis

Correlation analysis of immune regulatory genes comprising the IFNγ-associated gene signature, along with other statistical assessments, was performed using Stata version 19.5. Spearman's rank correlation method was applied to evaluate pairwise relationships between variables. Correlation matrix visualization was generated using the external package *heatplot*, installed from the official SSC repository (ssc install heatplot). Descriptive statistics for categorical variables were presented as absolute counts and percentages. Associations between gene signature expression and categorical variables were tested using the χ^2 test. Overall survival and prognostic value of clinicopathological and molecular factors were assessed using Kaplan–Meier survival analysis, the log-rank test, and multivariate Cox proportional hazards regression. For each prognostic factor, hazard ratios (HRs), p-values, and 95 % confidence intervals (CIs) were reported. Forest plots were generated to visualize Cox model results. Statistical significance was defined as $p < 0.05$.

Research results and their discussion.

Correlation analysis of IFNγ gene signature expression

To evaluate the coherence of gene expression within the IFNγ-associated signature, Spearman correlation analysis was performed. All ten analyzed genes – CXCL9, CXCL10, CXCL11, IDO1, IRF9, CCR5, STAT1, PRF1, IFNG, and HLA-DRA – are considered key components of the IFNγ-activated signaling cascade.

The results were visualized as a heatmap (Fig. 2), displaying the Spearman correlation coefficients (ρ) between all gene pairs and their association with the composite IFNγ signature score. The highest positive correlations with the overall signature score were observed for IDO1 (ρ=0.74), CXCL9, CXCL11, and CXCL10 (all ρ=0.40), indicating the leading contribution of these genes to the signature. Most gene pairs exhibited weak to moderate positive correlations ($\rho > 0$), while a few showed weak negative correlations (e.g., CXCL9 and STAT1: $\rho = -0.34$; IRF9 and CCR5: $\rho = -0.37$).

Overall, the findings support the conclusion that the IFNγ signature reflects coordinated transcriptional regulation of key immune response genes, including chemokines, transcription factors, and effector molecules. The high degree of inter-gene coherence – especially among IDO1 and the CXCL family – underscores the reliability of the signature as an integrated biomarker of IFNγ pathway activation.

Patient characteristics

The study analyzed the clinicopathological and molecular genetic characteristics of 419 patients with lung squamous cell carcinoma in relation to the expression levels of the IFNγ-associated gene signature. Patients were stratified into two groups based on the expression level of the gene signature: low expression (n=196) and high expression (n=223) (Tabl. 1).

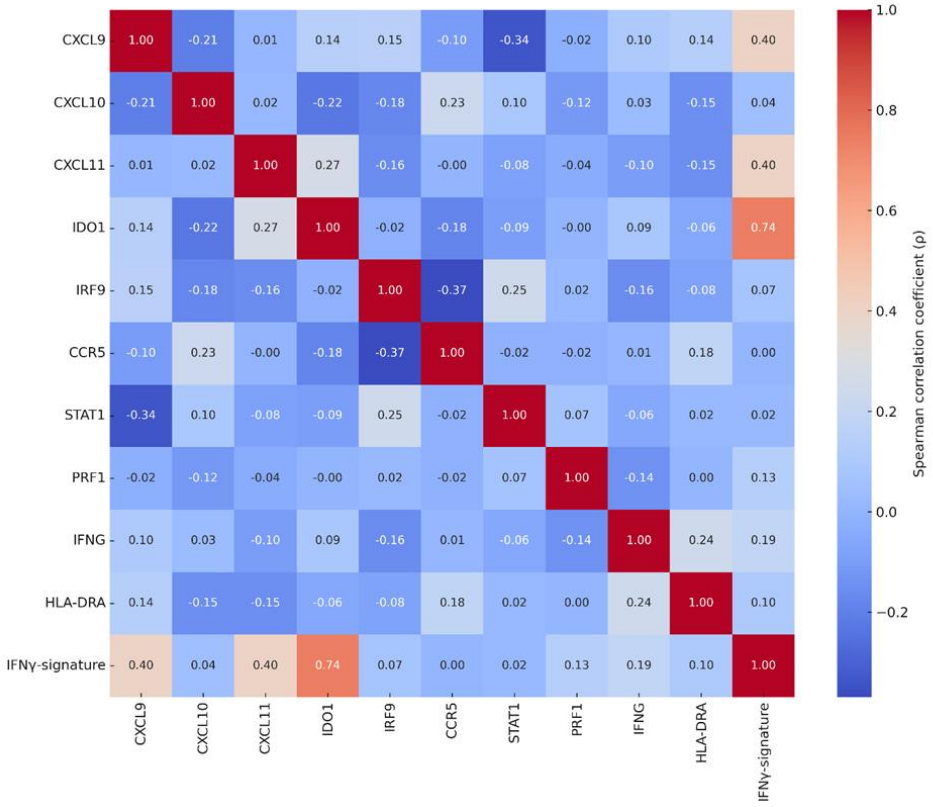

Fig. 2. Heatmap illustrating the correlation among CXCL9, CXCL10, CXCL11, IDO1, IRF9, CCR5, STAT1, PRF1, IFNG, and HLA-DRA gene expressions

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Table 1

Clinicopathological and molecular genetic characteristics of patients with LUSC and their association with the expression of the IFNγ-associated gene signature

Variables	Total, n=419	Low expression of the IFNγ-associated gene signature, n=196	Hight expression of the IFNγ-associated gene signature, n=223	p
Age (years), n (%) Medium <60 ≥60	67.0±8.53 82 (19.4) 337 (80.4)	65.0±9.98 38 (19.4) 158 (80.6)	65.5±10.17 44 (19.7) 179 (80.3)	0.930
Sex, n (%) Female Male	106 (25.3) 313 (74.7)	51 (26.0) 145 (74.0)	55 (24.7) 168 (75.3)	0.750
Stage, n (%) I II III IV Unknown	181 (43.2) 124 (29.6) 58 (13.8) 5 (1.2) 51 (12.2)	76 (38.8) 64 (32.7) 28 (14.3) 3 (1.4) 25 (12.8)	105 (47.1) 60 (26.9) 30 (13.5) 2 (0.8) 26 (11.7)	0.503
TTN mutation, n (%) Present Absent	356 (85.0) 63 (15.0)	164 (83.7) 32 (16.3)	192 (86.1) 31 (13.9)	0.488
TP53 mutation, n (%) Present Absent	377 (90.0) 42 (10.0)	177 (90.3) 19 (9.7)	200 (89.7) 23 (10.3)	0.833
KEAP1/NFE2L2 mutation, n (%) Present Absent	117 (27.9) 302 (72.1)	37 (18.9) 159 (81.1)	80 (35.9) 143 (64.1)	<0.00 01
PIK3CA mutation, n (%) Present Absent	56 (13.4) 363 (86.6)	29 (14.8) 167 (85.2)	27 (12.1) 196 (87.0)	0.420

The mean age of patients was 67.0 ± 8.53 years, with no statistically significant difference between the low and high IFNγ expression groups ($p = 0.930$). Similarly, there was no significant association between IFNγ signature expression and patient sex ($p = 0.750$) or tumor stage ($p = 0.503$). Mutations in TTN, TP53, and PIK3CA genes also showed no association with IFNγ signature expression levels ($p > 0.05$ for all comparisons).

In contrast, mutations in KEAP1 or NFE2L2 were significantly more frequent in patients with high IFNγ signature expression (35.9 % vs. 18.9 % in the low-expression group, $p < 0.0001$). This association may suggest a potential role of these mutations in shaping the tumor immune microenvironment.

Survival analysis

To evaluate the relationship between IFNγ-associated gene signature expression and overall survival in patients with lung squamous cell carcinoma, Kaplan–Meier survival analysis followed by the log-rank test was performed.

In the low-expression group, the median overall survival was 44.8 months, compared to 55.2 months in the high-expression group. Despite the observed difference in median survival, the log-rank test did not identify a statistically significant difference between the groups ($\chi^2(1)=0.37$; $p = 0.5453$), indicating no association between IFNγ signature expression level and overall survival in this cohort (Fig. 3).

To assess the independent impact of clinicopathological and molecular genetic variables on overall patient survival, a Cox proportional hazards regression analysis was performed using the Breslow method (Fig. 4).

The most significant prognostic factors were mutations in the TP53 and TTN genes. Specifically, the presence of a TP53 mutation was associated with a reduced risk of death (HR = 0.53; 95 % CI: 0.33–0.85; $p = 0.009$), as was the presence of a TTN mutation (HR = 0.58; 95 % CI: 0.40–0.85; $p = 0.005$), suggesting a potential protective effect of these mutations in this cohort.

Other variables, including age, sex, disease stage, mutations in PIK3CA and KEAP1/NFE2L2, and the level of IFNγ-associated gene signature expression, did not show a statistically significant association with overall survival ($p > 0.05$ for all variables). In particular, the IFNγ signature was not an independent prognostic factor (HR = 0.94; 95 % CI: 0.70–1.28; $p = 0.711$).

In this study, we evaluated the relationship between the expression of the IFNγ-associated gene signature and clinicomolecular characteristics in patients with lung squamous cell carcinoma (LUSC), based on data from the TCGA-LUSC project. Although the IFNγ signature showed a notable correlation with KEAP1/NFE2L2 mutational status, it was not identified as an independent prognostic factor for survival. These findings provide grounds for further investigation into the role of the IFNγ signaling pathway within the immune microenvironment of LUSC.

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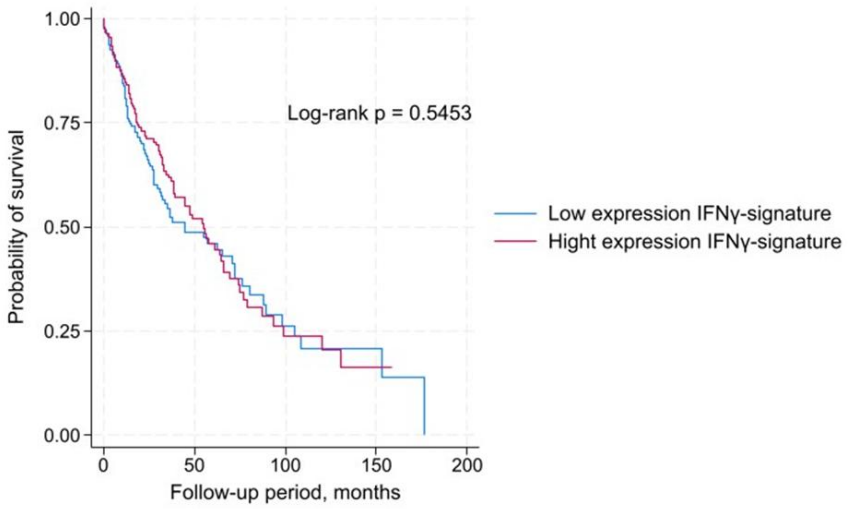

Fig. 3. Kaplan–Meier survival curves for patients with lung squamous cell carcinoma stratified by IFNγ-associated gene signature expression levels

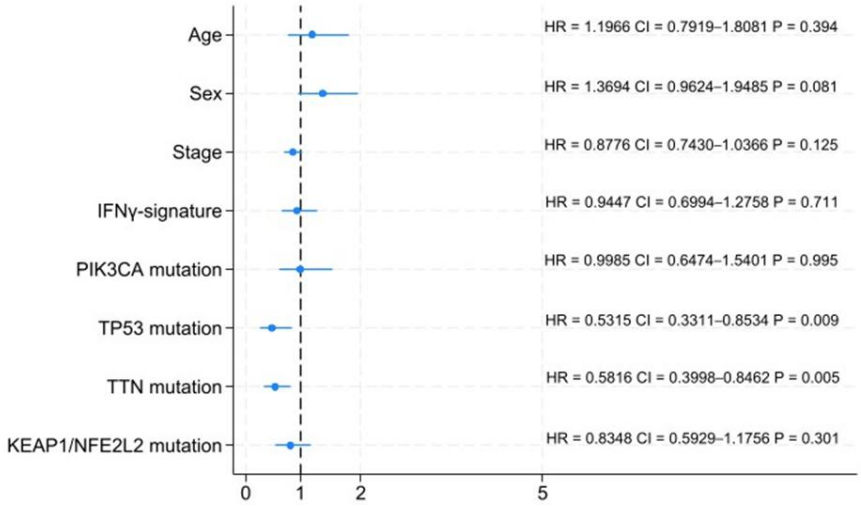

Fig. 4. Forest plot showing the effect of factors associated with overall patient survival in the Cox regression model. The vertical dashed line represents the neutral hazard ratio value (HR = 1), indicating no effect of the variable on mortality risk

Our results align with previous studies demonstrating that IFNγ-associated genes (e.g., CXCL9, CXCL10, IDO1) are key mediators of antitumor responses, promoting T cell recruitment and creating an immunologically favorable context for ICI therapy. In particular, Papalexi et al. [15] revealed that these genes actively regulate inhibitory immune checkpoints and may shape tumor responsiveness to immunotherapy by fostering a "highly immunogenic" phenotype. In our analysis, high expression levels of CXCL9, CXCL10, and IDO1 were most strongly correlated with the overall IFNγ signature, reaffirming their pivotal contribution.

An intriguing observation was the significantly higher frequency of KEAP1/NFE2L2 mutations among patients with elevated IFNγ signature expression. This finding supports the hypothesis of immunometabolic interactions, as discussed by Xu et al. [16], who showed that KEAP1-mutant tumors often exhibit oxidative stress, which can activate antiviral signaling cascades, including IFNγ. Therefore, KEAP1/NFE2L2 mutations may contribute to increased immune infiltration and IFNγ-driven responses. In the context of LUSC, where these mutations are relatively common, such insights may have practical relevance for predicting immunotherapy responsiveness.

Nonetheless, the IFNγ signature did not emerge as an independent prognostic factor in our cohort. This contrasts with findings in other lung cancer subtypes –particularly adenocarcinoma – where high IFNγ signature levels have been associated with prolonged survival [17, 18]. It is possible that other immunoregulatory mechanisms play a more dominant role in LUSC. For instance, Shi et al. [19] highlighted the significance of MAIT cells in determining ICI response, which may function independently of IFNγ signaling.

Another plausible explanation for the lack of prognostic relevance of the IFNγ signature may involve

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tumor hypoxia. Robles-Oteíza et al. [20] demonstrated that hypoxic conditions can suppress IFNγ-related signaling and promote acquired resistance to ICIs – even in immunologically active tumors. Given the frequent hypoxia in LUSC, particularly in central tumor masses, this could partially account for the weak association between the IFNγ signature and survival outcomes.

From a clinical perspective, it is noteworthy that mutations in TP53 and TTN, unlike the IFNγ signature, were independently associated with improved survival in our Cox regression model. These findings are partially consistent with data from Liu et al. [21], who reported that TTN mutations shape a distinct transcriptomic landscape characterized by immune activation. Qi et al. [22] also emphasized the role of TTN-associated long noncoding RNAs in modulating tumor progression and the immune microenvironment. In our cohort, TTN mutations may have reflected increased immune pressure, thereby contributing to better outcomes.

From a practical standpoint, it is important to emphasize that the IFNγ signature should not be considered an isolated biomarker. Its effectiveness likely depends on integration with other tumor characteristics, including mutational status, hypoxia, the presence of specific T-cell subsets, or mature tertiary lymphoid structures [18]. Comprehensive approaches – such as multimodal single-cell analyses [15] – may provide a deeper understanding of the biological mechanisms underlying ICI response in LUSC.

Finally, emerging therapeutic strategies targeting or modulating the IFNγ pathway merit attention. Notably, CAR-T cell–derived exosomes described by Zheng et al. [23] can simultaneously deliver cytotoxic agents and induce local immune responses through IFNγ activation. These combined approaches may be particularly effective for patients with high IFNγ signature expression who do not respond to conventional immunotherapy.

Thus, our study contributes to the existing body of evidence on the complex role of the IFNγ-associated gene signature in lung squamous cell carcinoma. Although it did not emerge as an independent prognostic factor, its association with KEAP1/NFE2L2 mutations and key immune genes indicates a potential role in shaping the tumor immune microenvironment [24].

This study has several limitations. First, the analysis was based on retrospective data from TCGA, limiting the generalizability of the findings to broader populations. Second, we did not account for the effects of treatment, temporal changes in the immune microenvironment, or the influence of other immune cell populations that may critically modulate IFNγ signaling. Third, the method used to quantify the IFNγ signature was relatively simple and did not reflect the full functional activity of the signaling cascade. Future prospective studies are needed to validate and extend these findings.

Conclusions. The IFNγ-associated gene signature demonstrates strong internal consistency and a statistically significant association with KEAP1/NFE2L2 mutations in lung squamous cell carcinoma. However, its expression level was not associated with key clinicopathological characteristics or patient survival and did not serve as an independent prognostic factor in multivariate analysis. These results suggest that the IFNγ signature reflects immune activation within the tumor microenvironment, yet its prognostic utility in LUSC remains limited. Further research is needed to clarify its role, accounting for tumor spatial heterogeneity, immune context, and treatment-related effects.

Prospects for further researches. We plan to investigate the prevalence of driver mutations in a cohort of surgically treated patients with non-small cell lung cancer.

Conflict of interest: absent.

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ПРОГНОСТИЧНА ЦІННІСТЬ IFNγ-АСОЦІЙОВАНОГО ГЕННОГО ПІДПИСУ ПРИ ПЛОСКОКЛІТИННІЙ КАРЦИНОМІ ЛЕГЕНЬ: ДАНІ TCGA

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Резюме. Плоскоклітинна карцинома легень є другим за поширеністю підтипом недрібноклітинного раку легень і характеризується високим мутаційним навантаженням та значною імунною інфільтрацією, що відкриває перспективні можливості для імунотерапії. Водночас відповідь на лікування залишається варіабельною, що підкреслює необхідність надійних біомаркерів. У цьому дослідженні було проаналізовано прогностичну цінність IFNγ-асоційованого генного підпису – транскриптомного індикатора імунної активності, що включає 10 ключових генів (CXCL9, CXCL10, CXCL11, IDO1, IRF9, CCR5, STAT1, PRF1, IFNG, HLA-DRA).

Було використано дані 419 пацієнтів із проєкту TCGA-LUSC. Пацієнтів стратифікували на групи з високою та низькою експресією IFNγ-підпису на основі порогового значення, визначеного ROC-аналізом (поріг: 7,32 $\log_2$(RSEM+1)). Статистичний аналіз проводили в середовищі Stata 19.5 з рівнем значущості $p<0,05$.

IFNγ-підпис продемонстрував високу внутрішню кореляцію, особливо для IDO1, CXCL9 та CXCL10. Хоча не було виявлено асоціації з віком, статтю, стадією пухлини або мутаціями у TP53, TTN чи PIK3CA, спостерігалася достовірна кореляція з мутаціями KEAP1/NFE2L2 ($p<0,0001$), що вказує на потенційну взаємодію між метаболічними й імунними механізмами.

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Аналіз виживаності не продемонстрував статистично значущої різниці між групами експресії IFNγ-підпису (p=0,5453). Результати регресії Кокса підтвердили, що IFNγ-підпис не є незалежним прогностичним чинником (HR=0,94; p=0,711), тоді як мутації TP53 та TTN асоціювалися з кращими клінічними результатами.

Ці дані свідчать, що, незважаючи на здатність IFNγ-підпису відображати імунну активацію в мікрооточенні пухлини, він не має незалежної прогностичної цінності при плоскоклітинній карциномі легень. Необхідні подальші дослідження, спрямовані на вивчення просторової гетерогенності пухлини, впливу лікування, складу імунних клітин, функціональної активності шляху IFNγ та його взаємодії з іншими механізмами резистентності до імунотерапії.

Ключові слова: IFNγ-асоційований генний підпис, плоскоклітинна карцинома легень, імунотерапія, прогнозування, біомаркер.

Конфлікт інтересів: відсутній.

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