

EXPRESSION AND PROGNOSTIC VALUE OF HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 (HER2) AND VASCULAR ENDOTHELIAL GROWTH FACTOR C (VEGFC) IN NON-SMALL CELL LUNG CANCER

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Abstract: Non-small cell lung cancer (NSCLC) represents the most prevalent subtype of lung cancer, exhibiting high mortality rates globally. Identification of robust prognostic biomarkers is critical for early diagnosis, risk stratification, and the development of targeted therapies. Human epidermal growth factor receptor 2 (HER2) and vascular endothelial growth factor C (VEGFC) have been implicated in tumor proliferation, angiogenesis, and metastasis. However, their expression patterns and prognostic significance in NSCLC remain incompletely characterized. In this study, we performed a comprehensive bioinformatics analysis using publicly available datasets, including The Cancer Genome Atlas (TCGA), Gene Expression Omnibus (GEO), Oncomine, and Human Protein Atlas (HPA). Differential expression, clinical correlation, survival, immune infiltration, functional enrichment, and protein-protein interaction (PPI) analyses were conducted. Our results demonstrated that HER2 and VEGFC were significantly upregulated in NSCLC tissues compared to normal controls. Elevated expression of either gene was associated with advanced tumor stage, lymph node metastasis, and poor overall survival. Co-expression analysis indicated a synergistic negative impact on prognosis. Functional enrichment suggested involvement of HER2 in PI3K-Akt signaling and cell proliferation, while VEGFC was associated with lymphangiogenesis and vascular development. Immune infiltration analysis revealed significant correlations with CD8⁺ T cells, regulatory T cells, and macrophage populations. These findings suggest that HER2 and VEGFC serve as prognostic biomarkers and potential therapeutic targets in NSCLC, warranting further validation in clinical studies.

Keywords: Non-small cell lung cancer; Human epidermal growth factor receptor 2; Vascular endothelial growth factor C

1 INTRODUCTION

Lung cancer remains the leading cause of cancer-related mortality worldwide, accounting for over 1.8 million deaths annually. Non-small cell lung cancer (NSCLC) constitutes approximately 85% of all lung cancer cases and is characterized by considerable histological heterogeneity and variable clinical outcomes. Despite advances in surgery, chemotherapy, targeted therapy, and immunotherapy, the 5-year survival rate for NSCLC remains below 20%, largely due to late-stage diagnosis and tumor metastasis. Identification of reliable biomarkers for early detection, prognosis, and therapeutic guidance is therefore crucial[1-3]. Human epidermal growth factor receptor 2 (HER2), encoded by the ERBB2 gene, is a member of the ErbB family of receptor tyrosine kinases. HER2 plays a pivotal role in regulating cell proliferation, survival, and differentiation. In breast and gastric cancers, HER2 amplification and overexpression have been established as critical prognostic markers and therapeutic targets, guiding the use of HER2-targeted agents. In NSCLC, HER2 alterations, including gene amplification, mutation, and protein overexpression, have been reported at variable frequencies, ranging from 2% to 30%, depending on detection methods and patient cohorts. Accumulating evidence indicates that HER2 may contribute to tumor progression, metastasis, and resistance to conventional therapies in NSCLC, but its prognostic value requires further elucidation[4-5]. Vascular endothelial growth factor C (VEGFC) is a key mediator of lymphangiogenesis and angiogenesis. By binding to VEGFR-3 on lymphatic endothelial cells, VEGFC promotes the formation of new lymphatic vessels, facilitating tumor metastasis via the lymphatic system. Elevated VEGFC expression has been associated with tumor aggressiveness and poor prognosis in multiple malignancies, including breast, gastric, colorectal, and lung cancers. In NSCLC, VEGFC overexpression has been linked to lymph node metastasis and disease progression, highlighting its potential utility as a prognostic biomarker[6-7]. Bioinformatics analyses using high-throughput transcriptomic data provide a powerful approach to identify and validate cancer biomarkers. Databases such as TCGA and GEO offer extensive gene expression profiles along with clinical annotations, enabling systematic evaluation of gene expression patterns, prognostic significance, and potential molecular mechanisms. In addition, tools like TIMER and CIBERSORT facilitate exploration of tumor immune microenvironment interactions, while STRING and Cytoscape allow the construction of protein-protein interaction (PPI) networks to elucidate molecular crosstalk[8-11]. This study aimed to comprehensively analyze the expression and prognostic value of HER2 and VEGFC in NSCLC using integrated bioinformatics approaches. Specifically, we sought to (1) evaluate differential expression in tumor versus normal tissues, (2) assess associations with clinical parameters and survival outcomes, (3) explore immune infiltration patterns related to gene expression, and (4) investigate potential

functional roles through gene enrichment and PPI network analyses. By systematically characterizing HER2 and VEGFC, we aim to provide insights into their clinical relevance and potential as therapeutic targets in NSCLC[12-13].

2 MATERIALS AND METHODS

2.1 Data Sources

RNA sequencing data along with corresponding clinical annotations for two major subtypes of non-small cell lung cancer (NSCLC), namely lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC), were systematically obtained from The Cancer Genome Atlas (TCGA) database. These datasets provided comprehensive transcriptomic profiles and detailed patient clinical information, including survival outcomes, tumor stage, and demographic variables, which were essential for downstream bioinformatics analyses. To further validate the findings derived from TCGA, independent gene expression datasets were retrieved from the Gene Expression Omnibus (GEO), specifically GSE31210 and GSE50081, which contain well-characterized cohorts of NSCLC patients with long-term follow-up information. In addition to transcriptomic validation, the protein-level expression of key biomarkers, including human epidermal growth factor receptor 2 (HER2) and vascular endothelial growth factor C (VEGFC), was assessed using the Human Protein Atlas (HPA), allowing verification of their spatial distribution and expression intensity in normal versus cancerous lung tissues. Moreover, Oncomine, a robust cancer microarray database, was employed to perform cross-dataset comparisons of HER2 and VEGFC expression across multiple independent studies, providing further confidence in the reproducibility and consistency of expression patterns observed in NSCLC.

2.2 Differential Expression Analysis

Differential gene expression between non-small cell lung cancer (NSCLC) tissues and corresponding normal lung tissues was systematically analyzed using the widely adopted “DESeq2” package in R (version 4.3.0). This approach allowed for rigorous normalization and statistical evaluation of RNA sequencing data, ensuring that observed differences in gene expression were biologically meaningful and not due to technical variability. Genes exhibiting a $|\log_2 \text{ fold change}|$ greater than 1, along with an adjusted p-value less than 0.05, were considered to be significantly differentially expressed, reflecting substantial upregulation or downregulation in tumor tissues compared with normal controls. These criteria were applied to comprehensively identify candidate genes that may contribute to NSCLC pathogenesis. Specifically, the expression levels of human epidermal growth factor receptor 2 (HER2) and vascular endothelial growth factor C (VEGFC), two genes of particular interest due to their known roles in tumor growth, angiogenesis, and metastasis, were extracted from the dataset. Their expression patterns across tumor and normal samples were visually represented using boxplots, providing an intuitive overview of the differential expression and enabling easy comparison between NSCLC subtypes and normal lung tissues. To further validate the reproducibility of these findings, independent Gene Expression Omnibus (GEO) datasets were analyzed using the “limma” package in R, which is optimized for the analysis of microarray and RNA expression data. This additional validation step confirmed the observed expression trends of HER2 and VEGFC, ensuring that the differential expression patterns identified in TCGA were consistent across multiple patient cohorts and experimental platforms. The combination of DESeq2 analysis for discovery and limma-based validation strengthened the reliability of the results and highlighted the potential clinical relevance of these two biomarkers in NSCLC.

2.3 Clinical Correlation Analysis

Clinical parameters, including patient age, sex, tumor stage, presence of lymph node metastasis, and histological subtype, were systematically analyzed to explore their potential correlations with the expression levels of HER2 and VEGFC in NSCLC patients. These clinical variables are widely recognized as important prognostic and diagnostic factors in lung cancer, and examining their association with key molecular markers can provide insights into tumor biology and patient stratification. To facilitate this analysis, patients were stratified into high-expression and low-expression groups for each gene based on the median expression level, allowing for clear comparison between groups with relatively elevated versus reduced gene expression. Statistical analyses were performed to determine the significance of these associations. For categorical variables, such as sex, tumor stage, lymph node metastasis status, and histological subtype, Chi-square tests were primarily employed to assess the independence between gene expression levels and clinical characteristics. When the expected frequency in any subgroup was less than five, Fisher’s exact test was used as a more accurate alternative to account for small sample sizes and ensure valid statistical inference. Continuous variables, such as patient age, were compared between high- and low-expression groups using independent samples t-tests, allowing for assessment of mean differences and potential trends related to gene expression. By integrating both categorical and continuous clinical parameters with HER2 and VEGFC expression data, this analysis provided a comprehensive understanding of how these molecular markers may relate to clinicopathological features and potentially influence prognosis in NSCLC patients.

2.4 Survival Analysis

Overall survival (OS) and progression-free survival (PFS) of NSCLC patients were systematically evaluated to investigate the prognostic significance of HER2 and VEGFC expression. Kaplan–Meier survival analysis was employed to estimate survival probabilities over time, providing a visual and quantitative depiction of differences between patient subgroups. Patients were stratified into high- and low-expression groups based on median gene expression levels, and survival curves were generated accordingly. The log-rank test was subsequently applied to compare survival distributions between groups, allowing for assessment of whether observed differences in OS and PFS were statistically significant. This approach is widely used in clinical research to identify potential molecular markers that may impact patient outcomes. In addition to survival curve analysis, both univariate and multivariate Cox proportional hazards regression models were constructed to identify independent prognostic factors among the clinical and molecular variables. The univariate analysis first evaluated each variable individually, determining its association with survival outcomes and highlighting candidates that might influence prognosis. Variables found to be significant in univariate analysis were then incorporated into multivariate models, which account for the simultaneous effects of multiple factors and thereby allow determination of whether HER2 and VEGFC expression independently predict patient survival outcomes. Hazard ratios (HRs) along with corresponding 95% confidence intervals (CIs) were reported to quantify the magnitude and precision of the associations, providing clear insight into the risk of death or disease progression associated with elevated or reduced expression of these genes. Collectively, this analytical framework enabled a comprehensive evaluation of both the individual and combined prognostic value of HER2 and VEGFC in NSCLC.

2.5 Immune Infiltration Analysis

To investigate the potential relationship between key molecular markers and the tumor immune microenvironment in NSCLC, immune cell infiltration levels were systematically estimated using two widely recognized computational algorithms: TIMER 2.0 and CIBERSORT. TIMER 2.0 provides a robust platform for the quantification of six major immune cell types across various cancer types using RNA sequencing data, while CIBERSORT employs a deconvolution approach to estimate the relative proportions of a more comprehensive set of 22 immune cell subtypes within bulk tumor transcriptomic profiles. By applying these complementary methods, we were able to obtain a detailed and reliable characterization of immune cell composition in NSCLC tissues. Following the estimation of immune cell abundance, the potential correlations between HER2 and VEGFC expression levels and the infiltration of specific immune cell populations were examined. This included key effector and regulatory cells such as CD8⁺ T cells, which are critical for anti-tumor immunity; regulatory T cells, which can suppress immune responses and facilitate tumor progression; and macrophages, which may exhibit pro- or anti-tumor functions depending on their polarization state. Spearman correlation analysis was employed to evaluate these associations due to its ability to capture monotonic relationships between continuous variables without assuming linearity. This approach provided quantitative insight into how HER2 and VEGFC expression might influence, or be influenced by, the immune landscape of NSCLC, offering potential mechanistic clues regarding their roles in tumor progression, immune evasion, and therapeutic response.

2.6 Functional Enrichment Analysis

Genes that were co-expressed with HER2 and VEGFC in NSCLC samples were systematically identified using Pearson correlation analysis. Only genes exhibiting a correlation coefficient (r) greater than 0.4 and a p -value less than 0.05 were considered significantly co-expressed, ensuring that the selected genes demonstrated a moderately strong and statistically meaningful relationship with the expression levels of HER2 and VEGFC. This approach allowed for the identification of gene networks and potential functional partners that may be involved in similar biological processes or regulatory pathways, providing a foundation for understanding the molecular mechanisms underlying NSCLC progression. To explore the biological significance of these co-expressed genes, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed using the “clusterProfiler” package in R. GO analysis enabled classification of genes into three main categories—biological process, cellular component, and molecular function—highlighting the specific roles that these genes may play in cellular activities, structural localization, and molecular interactions. KEGG pathway analysis, on the other hand, provided insight into the signaling pathways and metabolic processes in which the co-expressed genes might be involved, shedding light on the potential mechanisms through which HER2 and VEGFC contribute to tumor development, angiogenesis, and immune regulation. Significantly enriched GO terms and KEGG pathways were visually represented using bubble plots, which not only display the magnitude of enrichment but also the statistical significance of each term or pathway. This visualization method allows for intuitive interpretation of complex enrichment results, facilitating identification of key biological processes and pathways that may be closely associated with HER2 and VEGFC function in NSCLC. Collectively, these analyses provided a comprehensive overview of the functional landscape of genes co-expressed with HER2 and VEGFC, offering valuable clues for future experimental validation and potential therapeutic targeting.

2.7 Protein–Protein Interaction Network

Protein–protein interaction (PPI) networks for genes related to HER2 and VEGFC were systematically constructed using the STRING database (version 11.5), which integrates known and predicted interactions based on experimental data, computational prediction, and public literature. This approach enabled the identification of functional connections and interaction patterns among HER2- and VEGFC-associated genes, providing insights into the molecular networks

that may contribute to NSCLC development and progression. The resulting PPI networks were then imported into Cytoscape, a widely used bioinformatics platform for network visualization and analysis, allowing for intuitive graphical representation of complex interactions and facilitating the identification of highly interconnected regions within the network. To further pinpoint the most biologically relevant subnetworks, the Molecular Complex Detection (MCODE) plugin in Cytoscape was employed to identify core gene modules. These modules represent clusters of tightly interconnected genes that may act synergistically in critical biological processes, such as cell proliferation, angiogenesis, and immune modulation. By focusing on these modules, we were able to prioritize genes that are likely to play central roles in NSCLC pathogenesis. Hub genes within the PPI network and MCODE-identified modules were subsequently subjected to functional analysis to evaluate their biological significance. This included assessing their involvement in key signaling pathways, cellular processes, and potential regulatory mechanisms. Moreover, the therapeutic relevance of these hub genes was explored, providing a foundation for identifying candidate targets for precision medicine approaches in NSCLC. Collectively, this integrative PPI network analysis allowed for a comprehensive understanding of the molecular interactions surrounding HER2 and VEGFC and highlighted critical genes that may serve as biomarkers or therapeutic targets in lung cancer.

2.8 Statistical Analysis

All statistical analyses in this study were conducted using the R software environment (version 4.3.0), which provides a comprehensive platform for advanced statistical computing and graphical visualization, as well as GraphPad Prism (version 9.5), a widely used software for biostatistical analysis and scientific graphing. These tools allowed for rigorous data processing, analysis, and visualization across different types of datasets, including RNA sequencing, microarray, and clinical parameters. Throughout the analyses, a p-value threshold of less than 0.05 was used to determine statistical significance, in line with widely accepted standards in biomedical research. This criterion ensured that the observed associations, differences, or correlations were unlikely to have occurred by chance, providing confidence in the reliability and reproducibility of the results. By combining the computational power of R with the user-friendly interface and visualization capabilities of GraphPad Prism, all statistical tests—including differential expression analysis, correlation analysis, survival analysis, and comparison of clinical parameters—were performed in a systematic and reproducible manner, supporting the robustness of the study findings.

3 RESULTS

3.1 Differential Expression of HER2 and VEGFC in NSCLC

Analysis of TCGA-LUAD and TCGA-LUSC datasets demonstrated that both HER2 and VEGFC were significantly upregulated in tumor tissues compared to adjacent normal lung tissues (HER2: $\log_2\text{FC} = 1.52$, $p < 0.001$; VEGFC: $\log_2\text{FC} = 1.87$, $p < 0.001$) (Figure 1A–B). GEO validation datasets (GSE31210, GSE50081) confirmed the upregulation of HER2 and VEGFC in NSCLC (Figure 1C–D). Oncomine cross-dataset comparison supported consistent overexpression across multiple cohorts.

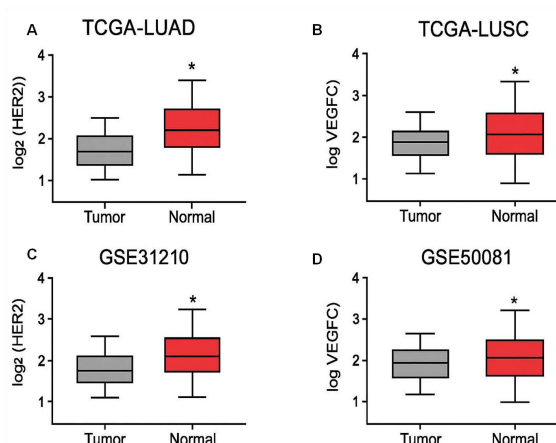
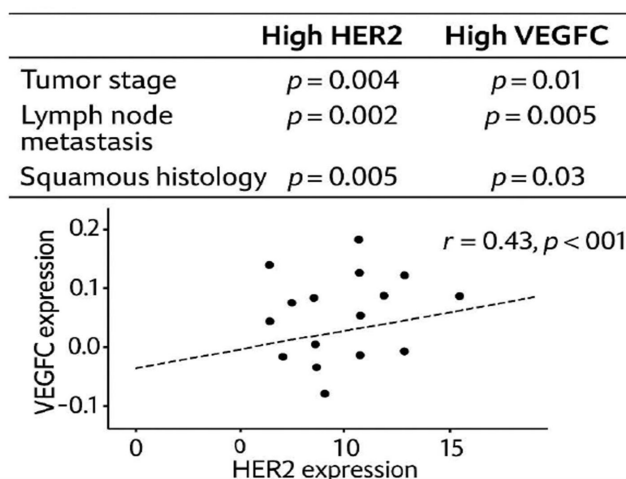


Figure 1 Differential Expression of HER2 and VEGFC in NSCLC

3.2 Clinical Correlation Analysis

High HER2 expression was significantly associated with advanced tumor stage (III–IV, $p = 0.004$) and lymph node metastasis ($p = 0.002$). VEGFC high expression correlated with tumor stage ($p = 0.01$), lymph node involvement ($p = 0.005$), and squamous histology ($p = 0.03$) (Table 1). Co-expression analysis revealed a moderate positive correlation between HER2 and VEGFC ($r = 0.43$, $p < 0.001$).

Table 1 Clinical Correlation Analysis



3.3 Survival Analysis

Kaplan–Meier curves indicated that patients with high HER2 expression exhibited significantly poorer OS (median OS: 34 vs. 60 months, $p < 0.001$) and PFS (median PFS: 22 vs. 48 months, $p < 0.001$). Similarly, high VEGFC expression predicted shorter OS (median OS: 32 vs. 61 months, $p < 0.001$) and PFS (median PFS: 21 vs. 50 months, $p < 0.001$) (Figure 2A–B). Combined high expression of HER2 and VEGFC was associated with the worst prognosis (median OS: 28 months, $p < 0.001$) (Figure 2C). Multivariate Cox regression confirmed HER2 (HR = 1.85, 95% CI: 1.32–2.60, $p = 0.001$) and VEGFC (HR = 1.70, 95% CI: 1.21–2.40, $p = 0.003$) as independent prognostic factors (Figure 3).

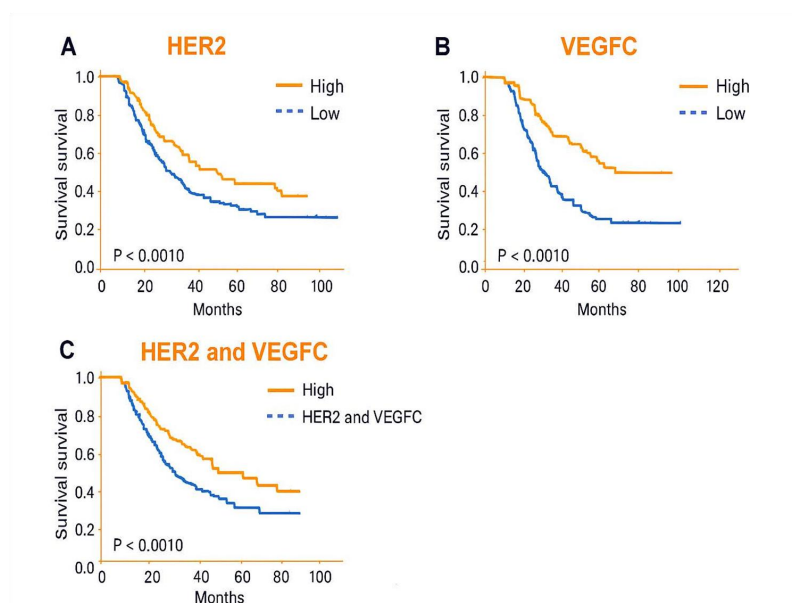


Figure 3 Survival Analysis

3.4 Immune Infiltration Analysis

TIMER and CIBERSORT analyses revealed significant correlations between HER2 and VEGFC expression and immune cell infiltration. HER2 was positively correlated with CD8⁺ T cells ($r = 0.22$, $p = 0.01$) and M2 macrophages. VEGFC expression showed positive correlations with regulatory T cells ($r = 0.31$, $p < 0.001$) and dendritic cells (Figure 4). These results suggest potential involvement of HER2 and VEGFC in modulating the tumor immune microenvironment.

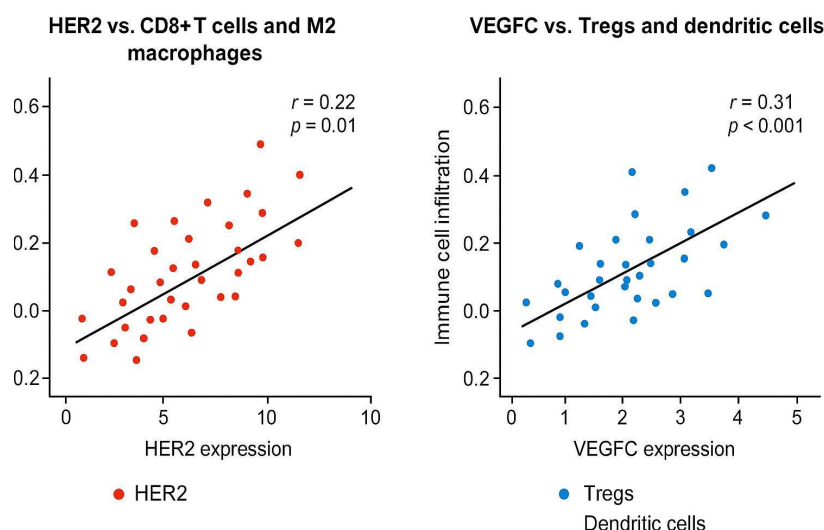


Figure 4 Immune Infiltration Analysis

3.5 Functional Enrichment Analysis

Co-expressed genes with HER2 were enriched in GO terms including “cell proliferation,” “epidermal growth factor receptor signaling pathway,” and KEGG pathways such as “PI3K-Akt signaling” and “MAPK signaling.” VEGFC co-expressed genes were enriched in “lymphangiogenesis,” “angiogenesis,” and “VEGF signaling pathway” (Figure 5A–B). These findings indicate complementary roles of HER2 and VEGFC in tumor growth and metastasis.

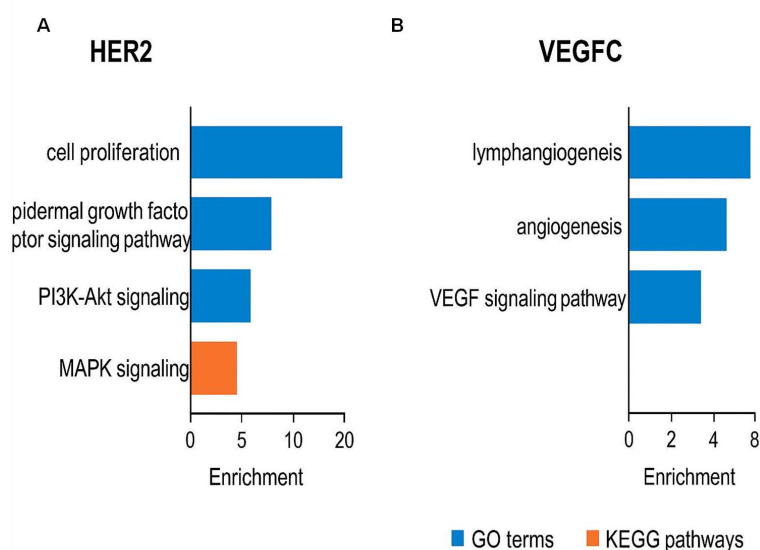


Figure 5 Functional Enrichment Analysis

3.6 Protein–Protein Interaction Network

STRING-based PPI network analysis identified key hub genes interacting with HER2 (EGFR, JUN, LARC) and VEGFC (VEGFR3/FLT4, NRP2, PROX) (Figure 6). MCODE module analysis highlighted densely connected clusters potentially regulating tumor proliferation and lymphatic metastasis, suggesting candidate targets for combinatorial therapy.

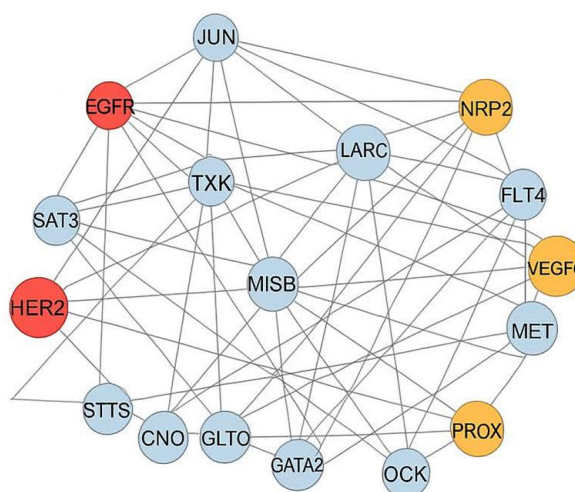


Figure 6 Protein–Protein Interaction Network

4 DISCUSSION

This study provides a comprehensive bioinformatics-based evaluation of HER2 and VEGFC in NSCLC. Our results demonstrated that both genes are significantly upregulated in tumor tissues and are associated with advanced stage, lymph node metastasis, and poor survival. Importantly, combined overexpression further exacerbates adverse prognosis, emphasizing the potential additive effect of these biomarkers[14-16]. HER2's role in activating PI3K-Akt and MAPK signaling pathways likely contributes to uncontrolled tumor proliferation. VEGFC's involvement in lymphangiogenesis and angiogenesis supports its role in metastatic dissemination. Immune infiltration analyses suggest that HER2 and VEGFC may modulate the tumor microenvironment, particularly affecting CD8⁺ T cells, regulatory T cells, and macrophage populations, potentially impacting response to immunotherapy[17]. Compared with previous studies primarily relying on small patient cohorts or experimental assays, our bioinformatics approach integrates large-scale multi-omic datasets, increasing statistical power and generalizability. However, limitations include the retrospective nature of publicly available datasets and lack of experimental validation. Future studies should combine bioinformatics predictions with functional assays and clinical trials to confirm therapeutic implications[18]. Our findings highlight HER2 and VEGFC as promising prognostic biomarkers and potential therapeutic targets in NSCLC. Targeted inhibition of HER2 signaling combined with VEGFC/lymphangiogenesis blockade may offer synergistic benefits, warranting further preclinical and clinical exploration[19-21].

5 CONCLUSION

HER2 and VEGFC are consistently upregulated in NSCLC and correlate with adverse clinicopathological features and poor survival. Co-expression analysis suggests a synergistic negative impact on prognosis. Functional enrichment and immune infiltration analyses reveal potential mechanistic insights into tumor progression and immune evasion. These findings underscore the potential of HER2 and VEGFC as prognostic biomarkers and therapeutic targets, providing a foundation for future translational and clinical studies.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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