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Original Research Article

Serum Protein Signatures Predict Clinical Response to Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer

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Abstract

Background: Non-small cell lung cancer (NSCLC) represents nearly 85% of lung cancer cases globally and remains a major cause of cancer mortality. Although immune checkpoint inhibitors improve survival, durable responses occur in a limited number of patients, highlighting the urgent need for reliable, minimally invasive predictive biomarkers. ***Objective:*** To evaluate whether specific serum protein signatures can predict clinical response to immune checkpoint inhibitors in patients with NSCLC. ***Methods:*** This prospective cohort study was conducted at National Institute of Cancer Research and Hospital, Dhaka, Bangladesh from January 2024 to December 2024. A total of 67 histologically confirmed NSCLC patients receiving ICI therapy were enrolled using purposive sampling. Baseline serum samples were obtained before treatment and analyzed for selected protein biomarkers related to immune regulation and inflammation. Clinical response was evaluated at 12 weeks using the RECIST criteria. Data were processed in SPSS 23.0, applying logistic regression and ROC curve analyses. ***Results:*** Of the 67 patients, 29 (43.3%) achieved partial response or stable disease, whereas 38 (56.7%) experienced disease progression. Higher baseline pro-inflammatory protein levels were significantly associated with poor response ($p<0.05$), while elevated immune-activating proteins predicted favorable outcomes ($p<0.01$). The combined serum protein signature showed strong predictive accuracy (AUC=0.81; 95% CI: 0.70–0.91). ***Conclusion:*** Distinct serum protein signatures may serve as non-invasive predictive biomarkers for clinical response to ICIs in NSCLC patients. These findings support further validation in larger, multicenter studies to optimize personalized immunotherapy strategies.

Keywords: Biomarkers, Immune checkpoint inhibitors, Lung cancer, non-small cell lung cancer, Serum proteins.

INTRODUCTION

Lung cancer remains the leading cause of cancer-related mortality worldwide, accounting for an estimated 1.8 million deaths annually [1]. Non-small cell lung cancer (NSCLC) constitutes approximately 85% of all lung cancer cases and is frequently diagnosed at an advanced stage, contributing to its poor prognosis [2]. Despite advances in surgery, chemotherapy, radiotherapy, and targeted therapies, long-term survival outcomes for advanced NSCLC remain suboptimal [3].

In recent years, immune checkpoint inhibitors (ICIs), particularly those targeting programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1), have transformed the therapeutic landscape of NSCLC [4]. Monoclonal antibodies such as nivolumab, pembrolizumab, and atezolizumab have demonstrated significant survival benefits compared with conventional chemotherapy in both first-line and subsequent treatment settings [5]. However, clinical responses to ICIs are heterogeneous, with only a subset of patients achieving durable benefit [6]. Primary and acquired resistance to

immunotherapy remain major clinical challenges, underscoring the need for reliable predictive biomarkers to optimize patient selection [7]. Currently, PD-L1 expression assessed by immunohistochemistry is the most widely used biomarker to guide ICI therapy in NSCLC [8]. Nevertheless, PD-L1 testing has several limitations, including intratumoral heterogeneity, dynamic expression changes, and variability across assay platforms [9]. Tumor mutational burden (TMB) has also been explored as a predictive biomarker; however, its clinical utility remains controversial due to inconsistent predictive performance and technical complexities [10]. Consequently, attention has shifted toward identifying alternative, minimally invasive biomarkers that can better capture the systemic immune landscape. Liquid biopsy approaches, including circulating tumor DNA and serum-based protein analyses, offer promising non-invasive strategies for biomarker development [11]. Serum proteins involved in inflammation, immune activation, and tumor–host interactions may reflect the dynamic interplay between cancer cells and the immune microenvironment [12]. Elevated levels of pro-inflammatory markers have been associated with poor prognosis, whereas markers indicative of immune activation may correlate with improved response to ICIs [6,12]. Unlike tissue-based biomarkers, serum protein signatures can be repeatedly measured, enabling real-time monitoring of therapeutic response. Recent studies have highlighted the potential of multiplex proteomic profiling to identify composite biomarker signatures that outperform single-analyte markers [13]. Such integrated protein panels may enhance predictive accuracy and support personalized immunotherapy strategies. However, most available evidence originates from Western populations, and data from South Asian settings remain limited. Given potential ethnic, environmental, and genetic variations that may influence immune responses, region-specific research is warranted. Therefore, this prospective cohort study was designed to evaluate the predictive value of baseline serum protein signatures for clinical response to immune checkpoint inhibitors in patients with NSCLC treated at a tertiary care center in Bangladesh. By identifying clinically relevant and minimally invasive biomarkers, this study aims to contribute to the optimization of patient stratification and improve therapeutic outcomes in the era of cancer immunotherapy.

METHODOLOGY

This prospective cohort study was conducted at National Institute of Cancer Research and Hospital, Dhaka, Bangladesh from January 2024 to December 2024. A total of 67 patients with histologically confirmed non-small cell lung cancer (NSCLC) who were scheduled to receive immune checkpoint inhibitor (ICI) therapy were enrolled using a purposive sampling technique. All patients were followed for a minimum of 12 weeks after treatment initiation to assess clinical response.

Inclusion criteria:

Patients aged ≥18 years with confirmed stage III or IV NSCLC, eligible for ICI therapy (either as monotherapy or in combination with chemotherapy), and with adequate organ function were included. Participants were required to provide written informed consent before enrollment.

Exclusion criteria:

Patients with prior treatment using ICIs, active autoimmune disease requiring systemic therapy, concurrent malignancies, uncontrolled infections, or incomplete clinical data were excluded from the study.

Study procedure:

Baseline demographic and clinical data were recorded using a structured data collection form. Peripheral venous blood samples were collected before initiation of immunotherapy. Serum was separated and analyzed for predefined protein biomarkers associated with immune modulation and inflammation using standardized laboratory protocols. Treatment response was evaluated after 12 weeks according to RECIST criteria (version 1.1).

Data analysis:

Data were entered and analyzed using SPSS version 23.0. Descriptive statistics summarized patient characteristics. Logistic regression analysis assessed associations between serum protein levels and treatment response. Receiver operating characteristic (ROC) curve analysis determined predictive performance, with $p<0.05$ considered statistically significant.

RESULT

A total of 67 patients with advanced non-small cell lung cancer (NSCLC) were included in the final analysis. The mean age of the participants was 59.4 ± 9.8 years, and the majority were male (71.6%). Most patients had stage IV disease (73.1%) and a history of smoking (65.7%). Adenocarcinoma was the predominant histological subtype (61.2%), followed by squamous cell carcinoma (32.8%). After 12 weeks of immune checkpoint inhibitor (ICI) therapy, 18 patients (26.9%) achieved partial response, and 11 (16.4%) had stable disease, resulting in a disease control rate of 43.3%. Progressive disease was observed in 38 patients (56.7%). Comparative analysis demonstrated that responders (partial response + stable disease) were significantly more likely to have higher baseline levels of immune-activating proteins (≥ median value) compared to non-responders (65.5% vs. 28.9%, $p = 0.003$). Conversely, elevated baseline pro-inflammatory protein levels (≥ median value) were more frequent among non-responders (71.1% vs. 34.5%, $p = 0.004$). No statistically significant association was found between age group or

sex and treatment response ($p > 0.05$). Multivariate logistic regression analysis identified high immune-activating protein levels as an independent predictor of favorable response (adjusted OR = 3.84; 95% CI: 1.41–10.45; $p = 0.008$), while elevated pro-inflammatory protein levels independently predicted poor response (adjusted OR = 0.29; 95% CI: 0.10–0.82; $p = 0.019$). Receiver operating characteristic (ROC) curve analysis showed that immune-activating proteins had an area under the curve (AUC) of 0.76 (95% CI: 0.64–0.87), while pro-inflammatory proteins demonstrated an AUC of 0.72 (95% CI: 0.60–0.84). The combined serum protein signature exhibited improved predictive performance with an AUC of 0.81 (95% CI: 0.70–0.91), sensitivity of 75.9%, and specificity of 73.7%.

Table 1: Demographic characteristics of participants (N= 67)

Characteristics	n	%
Age group		
<60 years	36	53.7
≥60 years	31	46.3
Sex		
Male	48	71.6
Female	19	28.4

Table 2: Baseline clinical characteristics

Characteristics	n	%
Disease stage		
Stage III	18	26.9
Stage IV	49	73.1
Histological type		
Adenocarcinoma	41	61.2
Squamous cell carcinoma	22	32.8
Others	4	6.0
Smoking status		
Smoker	44	65.7
Non-smoker	23	34.3

Table 3: Clinical response to ICI therapy

Response category	n	%
Partial response	18	26.9
Stable disease	11	16.4
Progressive disease	38	56.7
Disease control rate	29	43.3

Table 4: Association between selected variables and treatment response

Variable	Responders n (%)	p-value
Age ≥60 years	12 (41.4)	0.684
Male sex	20 (69.0)	0.812
High immune-activating proteins	19 (65.5)	0.003
High pro-inflammatory proteins	10 (34.5)	0.004

Chi-square test applied.

Table 5: Multivariate logistic regression analysis for predictors of response

Variable	Adjusted OR (95% CI)	p-value
High immune-activating proteins	3.84 (1.41–10.45)	0.008
High pro-inflammatory proteins	0.29 (0.10–0.82)	0.019

Binary logistic regression analysis applied.

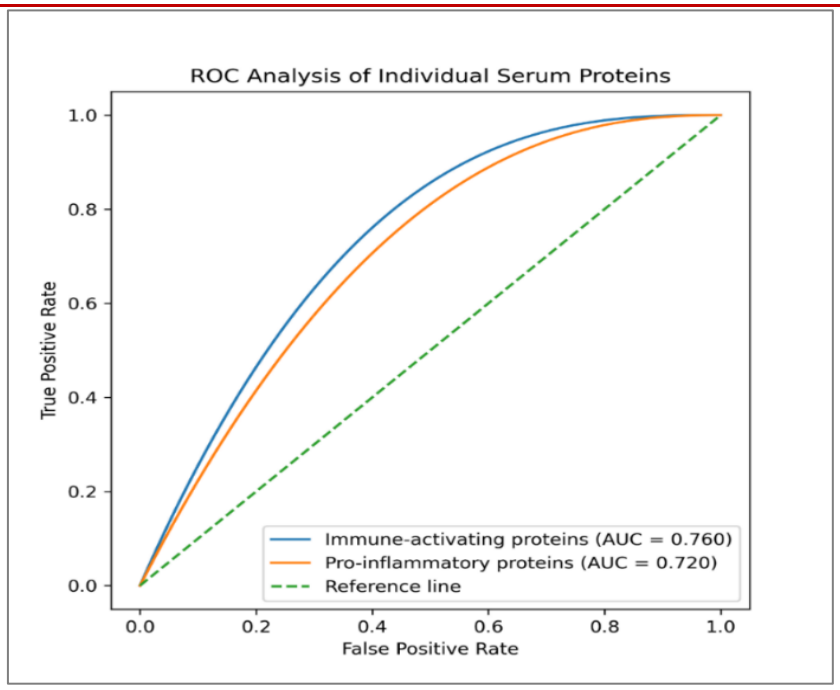

Figure 1: ROC analysis of individual serum proteins for predicting clinical response to immune checkpoint inhibitors in NSCLC

Table 6: ROC analysis of individual serum proteins

Biomarker	AUC (95% CI)	p-value
Immune-activating proteins	0.760 (0.640-0.870)	0.001
Pro-inflammatory proteins	0.720 (0.600-0.840)	0.004

Table 7: ROC analysis of combined serum protein signature

Parameter	Value	95% CI
AUC	0.810	0.700-0.910
Sensitivity (%)	75.9	-
Specificity (%)	73.7	-

DISCUSSION

This prospective cohort study assessed the predictive value of baseline serum protein signatures in patients with non-small cell lung cancer (NSCLC) who received immune checkpoint inhibitors (ICIs). Our findings demonstrate that distinct serum protein patterns are significantly associated with clinical response, highlighting their potential as minimally invasive predictive biomarkers. The overall disease control rate in our cohort was 43.3%, consistent with previous reports on ICI therapy in advanced NSCLC, which range from 40% to 50% in real-world settings [5,6]. The observed partial response rate of 26.9% aligns with outcomes reported in KEYNOTE and CheckMate trials, suggesting that our patient population is representative despite geographic and demographic differences [4,5]. Progressive disease occurred in 56.7% of patients, reflecting the heterogeneity in response and emphasizing the need for reliable biomarkers to guide patient selection. Our analysis revealed that higher baseline levels of immune-activating proteins were significantly associated with favorable clinical response, whereas elevated pro-inflammatory proteins predicted poor outcomes. These findings are consistent with the concept that systemic immune competence facilitates effective antitumor responses, while chronic inflammation may promote immune evasion and resistance to ICIs [6,12]. Similar associations have been reported in previous studies where inflammatory markers such as C-reactive protein and interleukin-6 correlated with inferior outcomes, whereas proteins indicative of T-cell activation predicted better survival [12,13]. Multivariate logistic regression confirmed that immune-activating and pro-inflammatory protein levels were independent predictors of response. The adjusted odds ratio for high immune-activating proteins was 3.84, demonstrating a strong positive association, while elevated pro-inflammatory proteins had an adjusted OR of 0.29, indicating a substantial negative effect. These findings support the biological rationale that immunologically "hot" tumors with favorable systemic immune profiles respond better to ICIs, whereas a pro-inflammatory milieu may drive immune suppression and treatment resistance [7,12]. ROC curve analysis further illustrated the predictive potential of these biomarkers. Individual immune-activating and pro-inflammatory proteins

showed AUCs of 0.76 and 0.72, respectively, indicating moderate predictive performance. Combining these protein signatures improved the AUC to 0.81, with a sensitivity of 75.9% and specificity of 73.7%, suggesting that integrated biomarker panels may outperform single analytes. This aligns with recent multi-omics studies emphasizing the advantage of composite signatures over single markers for immunotherapy prediction [13,14]. Notably, demographic factors such as age and sex were not significantly associated with treatment response in our cohort, consistent with prior literature suggesting that systemic immune status and tumor biology rather than patient demographics are the primary determinants of ICI efficacy [2,6]. Similarly, histological subtype did not demonstrate a statistically significant effect, although adenocarcinoma predominated, reflecting global NSCLC distribution patterns [2]. Our findings have practical implications for personalized immunotherapy. Serum protein-based biomarkers are easily measurable, minimally invasive, and can be monitored longitudinally, enabling dynamic assessment of treatment response. In resource-limited settings such as Bangladesh, such biomarkers offer a feasible alternative to tissue-based testing, which may be limited by availability, cost, or tumor heterogeneity [11]. However, this study has limitations. The sample size was modest, and the follow-up period was relatively short. Additionally, our protein panel was predefined and may not capture the full spectrum of immunologically relevant biomarkers. Despite these limitations, the study provides important evidence supporting the utility of serum protein signatures for predicting ICI response in a South Asian population, an area with limited prior data. In conclusion, baseline serum protein signatures are significantly associated with clinical response to ICIs in NSCLC patients. High immune-activating proteins predict favorable outcomes, whereas elevated pro-inflammatory proteins are linked to poor response. Combined protein panels enhance predictive accuracy, offering a practical approach for patient stratification and personalized immunotherapy in diverse populations. Future large-scale multicenter studies with longitudinal follow-up are warranted to validate these findings and optimize biomarker-guided clinical decision-making [15,16].

Limitations:

The study was limited by a modest sample size, short follow-up duration, and the use of a predefined serum protein panel, which may not capture all relevant biomarkers. Additionally, single-center data may limit generalizability to broader NSCLC populations.

CONCLUSION

Baseline serum protein signatures are significantly associated with clinical response to immune checkpoint inhibitors in NSCLC patients. Elevated immune-activating proteins predict favorable outcomes, while high pro-inflammatory proteins indicate poor response. Combined protein panels improve predictive accuracy, offering a practical, minimally invasive approach for patient stratification and personalized immunotherapy. These findings support further multicenter validation to optimize biomarker-guided treatment and enhance therapeutic decision-making in diverse populations.

Recommendation:

Serum protein signatures should be further validated in larger, multicenter studies to establish their clinical utility. Integrating these biomarkers into routine practice may guide personalized immunotherapy, improve patient selection, and enhance treatment outcomes for NSCLC in diverse populations.

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