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DIAGNOSTIC ACCURACY OF SERUM SQUAMOUS CELL CARCINOMA ANTIGEN AND CARCINOEMBRYONIC ANTIGEN IN DETECTING NON-SMALL CELL LUNG CANCER: A CROSS-SECTIONAL STUDY FROM SOKOTO, NORTHWESTERN NIGERIA

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Abstract

Background: Lung cancer is one of the leading causes of cancer incidence and cancer-related deaths globally. Late presentation, non-specific symptoms, and limited access to advanced imaging contribute to delayed diagnosis in Nigeria. Serum biomarkers such as squamous cell carcinoma antigen (SCC-Ag) and carcinoembryonic antigen (CEA) have been associated with non-small cell lung cancer (NSCLC), but their diagnostic accuracy remains uncertain.

Objective: To evaluate the diagnostic performance of serum SCC-Ag and CEA, individually and in combination, for detecting NSCLC.

Methods: This prospective cross-sectional study recruited patients with suspected primary lung cancer at Usmanu Danfodiyo University Teaching Hospital, Sokoto, from February 2022 to February 2023. All participants underwent tissue biopsy and serum assays for SCC-Ag and CEA using enzyme-linked immunosorbent assay (ELISA). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and receiver operating characteristic (ROC) curves were computed.

Results: Twenty-two patients completed the study; 16 (72.7%) had NSCLC. SCC-Ag demonstrated high sensitivity (93.8%) but low specificity (28.6%). CEA showed moderate sensitivity (50%) and specificity (42.8%). The combination of SCC-Ag and CEA achieved 100% sensitivity but only 42.9% specificity. All biomarkers had poor diagnostic accuracy, with AUC values below 0.7.

Conclusion: Although SCC-Ag and combined biomarkers showed high sensitivity, their low specificity and poor overall accuracy limit their use for NSCLC diagnosis in clinical practice. Larger studies are recommended.

Keywords: *Non-small cell lung cancer, serum biomarkers, squamous cell carcinoma antigen, carcinoembryonic antigen, diagnostic accuracy.*

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Introduction

Lung cancer is one of the leading causes of cancer incidence and cancer-related mortality worldwide, responsible for 12.4% of cancer diagnoses and 18.7% of cancer deaths.[1] In Nigeria, the incidence is low, at about 1.3%, compared with that in Western countries and in South and North African countries.[1] However, the absence of a national registry contributes to an underestimation of the disease burden, even as recent reports show an increasing incidence.[2]

Lung cancer is classified into two major histological categories: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). Adenocarcinoma (ADC) and squamous cell carcinoma (SCC) are the two principal histologic subtypes of non-small cell lung cancer (NSCLC), distinguished by histopathological and molecular characteristics. An elevated risk of lung cancer correlates with numerous epidemiological and environmental factors. Nonetheless, these risk factors exhibit disparities among patients from different racial and cultural backgrounds. Notably, diverse populations exhibited unique molecular characteristics, as demonstrated by differences in genetic mutation profiles. Additionally, various histological and molecular progression patterns in lung cancer have been recognised, which may be essential for improving diagnosis, prognosis, and treatment strategies.[3]

Most patients present with advanced disease due to non-specific early symptoms, limited screening capacity, and delayed diagnosis.[2, 4] While low-dose computed tomography is effective for screening high-risk individuals, its cost and high false-positive rates limit its use in low-resource settings.[5, 6] Tissue biopsy remains the diagnostic gold standard, but may be invasive or unsafe in critically ill patients.[7]

Serum biomarkers offer a minimally invasive alternative. Elevated levels of squamous cell carcinoma antigen (SCC-Ag) and carcinoembryonic antigen (CEA) have been reported in NSCLC.[8] However, their diagnostic reliability remains uncertain, especially in African populations.[9, 10]

This study aims to evaluate the diagnostic accuracy of serum SCC-Ag and CEA in detecting NSCLC.

Methods

This was a hospital-based prospective cross-sectional study. It was conducted from February 2022 to February 2023 at a tertiary healthcare centre serving residents of at least 3 northwestern states. The sample size was determined using the Cochrane formular ($n = \frac{[Z_{1-\alpha/2}]^2 pq}{(d)^2}$) and the modified formular for finite populations ($n_f = \frac{n}{1+\frac{n}{N}}$). where:

$Z_{1-\alpha/2}$ (standard normal variate at 5% type I error) is 1.96,

p (previous study biomarker sensitivity) is 0.8,

q (complementary probability, 1-p) is 0.2 and d (margin of error) is 0.05.

N (average number of lung cancers seen in the 3 previous years in our facility) and n (calculated sample size).

The estimated sample size was 20, and after accounting for a 10% non-response rate, the final sample size was 22.

Study Population:

Patients who are 35 years and above, have symptoms suggestive of primary lung cancer (cough, dyspnoea, haemoptysis, and weight loss), have radiological evidence suggestive of primary lung cancer and those with

histologically confirmed primary lung cancer were included. Whereas, patients with a history of previous lung cancer treatment, evidence of extrapulmonary malignancy or metastasis from another primary site were excluded from the study.

Procedures:

Consecutive patients were evaluated clinically and radiologically, including a detailed history, physical examination and chest examination. A radiologist reviewed all radiological images. Each patient underwent a standard CT-assisted percutaneous transthoracic biopsy using a size 16G Tru-Cut needle under an aseptic technique. The study employed a convenience sampling approach due to the relatively small number of patients presenting with suspected primary lung malignancy during the study period. Tissue biopsy specimens were fixed in 10% buffered formalin, processed routinely, embedded in paraffin wax, sectioned, and stained with haematoxylin and eosin. Consultant pathologists independently reviewed histopathologic diagnosis to confirm the presence and subtype of non-small cell lung cancer. Similar histopathologic processing methods have been described in contemporary thoracic oncology studies evaluating diagnostic biomarkers in NSCLC.[11]

Ten (10) millilitres of venous blood were collected under aseptic conditions into plain sample bottles and allowed to clot at room temperature. Samples were centrifuged at 3000 rpm for 10 minutes, and serum was separated and stored at −20°C until analysis. Serum SCC-Ag and CEA levels were analysed by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions, using the Rayto RT 2100C microplate reader (Parsbiochem, China). Biomarker positivity thresholds were based on the manufacturer's reference ranges. These specimen-handling and ELISA-processing methods are consistent with recommendations from recent biomarker validation studies.[12]

Data Analysis:

The data were analysed using Statistical Package for the Social Sciences (SPSS) version 25. Continuous variables were assessed for normality using visual inspection and the Shapiro–Wilk test. Since biomarker levels were not normally distributed, results were summarised using medians and interquartile ranges, while comparisons were performed using the Mann–Whitney U test. Correlation analysis was also performed to assess associations between biomarker levels and histologic diagnosis. Receiver operating characteristic (ROC) curve analysis was used to determine diagnostic performance.[13] ROC curves were used to evaluate accuracy; an AUC ≤ 0.7 was considered poor.[14]

Results

Clinical Characteristics:

The median age was 60 years (IQR: 47.3–75.0). Most participants were over 40 years old. The NSCLC group had a male-to-female ratio of 4.3:1.

Histological Findings: Sixteen participants (72.7%) had NSCLC; six had benign disease, including tuberculosis, bronchiectasis, and non-specific inflammation (Table II)

Table I. Clinical Characteristics of Study Participants (N = 22)

Variable	Yes. n (%)	No n (%)
Cough	21 (95.5)	1 (4.5)
Dyspnoea	18 (81.8)	4 (18.2)
Haemoptysis	5 (22.7)	17 (77.3)
Chest pain	8 (36.4)	14 (63.6)
Weight loss	11 (50.0)	11 (50.0)
Cigarette smoking	9 (40.9)	13 (59.1)
Chemical exposure	4 (18.2)	18 (81.8)
Previous tuberculosis	3 (13.6)	19 (86.4)
Cachexia	10 (45.5)	12 (54.5)
Digital clubbing	6 (27.3)	16 (72.7)
Abnormal chest examination	18 (81.8)	4 (18.2)
Abnormal radiologic finding	22 (100)	0
Pleural effusion	15 (68.2)	7 (31.8)

Table II. Histological Diagnosis of Participants

Histological Diagnosis	Frequency (n = 22)	Percentage (%)
NSCLC	16	72.7
Benign disease	6	27.3

NSCLC – non-small cell lung cancer

Serum Biomarker Levels:

SCC-Ag was elevated in 93.8% of NSCLC cases but also in 66.7% of benign conditions. CEA was elevated in 61.5% of adenocarcinoma cases and in 50% of benign conditions There were no statistically significant differences in biomarker medians ($p > 0.05$). SCC-Ag- Squamous cell carcinoma antigen, CEA- Carcinoembryonic antigen, NSCLC – non-small cell lung cancer

Table III. Serum Biomarker Levels in NSCLC vs Benign Disease

Variable	NSCLC Median (IQR)	Benign Median (IQR)	Test Statistic (MWU)	p-value
SCC-Ag (ng/mL)	3.82 (3.19–4.47)	4.11 (2.72–4.63)	44.500	0.796
CEA (ng/mL)	4.38 (2.75–9.47)	7.16 (2.189–254.11)	38.000	0.461
SCC-Ag + CEA	8.92 (6.37–13.17)	13.10 (5.38–258.64)	31.000	0.210

Correlation With Histology:

Biomarker levels showed poor correlation with histologic diagnosis.

Table IV. Correlation Between Serum Biomarkers and Histological Diagnosis

Variable	Correlation Coefficient (r)	*p*-value
SCC-Ag	0.241	0.280
CEA	0.131	0.561
SCC-Ag + CEA	0.135	0.549

SCC-Ag- Squamous cell carcinoma antigen,
CEA- Carcinoembryonic antigen,

Diagnostic Performance:

SCC-Ag had high sensitivity but low specificity.

CEA demonstrated moderate sensitivity and low specificity.

Combined biomarkers had excellent sensitivity but poor specificity.

Table V. Diagnostic Performance of Serum Biomarkers

Diagnostic Indicator	SCC-Ag	CEA	Combined (SCC-Ag + CEA)
Sensitivity	0.938	0.500	1.000
Specificity	0.286	0.428	0.429
Positive Predictive Value (PPV)	0.750	0.666	0.800
Negative Predictive Value (NPV)	0.666	0.273	1.000

Table VI. Association Between Biomarker-Based Diagnosis and Histology

Biomarker	Histology		Fisher's exact	*p*-value
	NSCLC	Benign		
SCC-Ag			2.718	0.169
NSCLC	15 (93.8%)	4 (66.7%)		
Benign	1 (6.2%)	2 (33.3%)		
CEA			0.489	0.646
NSCLC	8 (50%)	4 (66.7%)		
Benign	8 (50%)	2 (33.3%)		
SCC-Ag + CEA			9.263	0.013
NSCLC	16 (100%)	3 (50%)		
Benign	0	3 (50%)		

SCC-Ag- Squamous cell carcinoma antigen,
CEA- Carcinoembryonic antigen,
NSCLC – non-small cell lung cancer

Receiver Operating Characteristics (ROC) Analysis

All biomarkers demonstrated poor diagnostic accuracy due to low AUC values (<0.7).

The ROC curves compare the diagnostic accuracy of SCC-Ag, CEA, and their combined use in detecting NSCLC. All three biomarkers demonstrated poor diagnostic performance, with AUC values below 0.7.

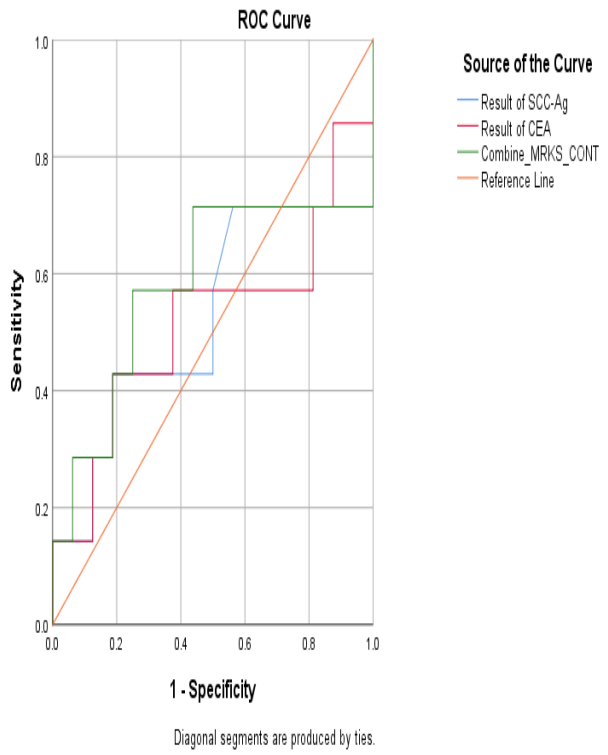

Figure 1. ROC Curves for SCC-Ag, CEA, and Combined Biomarkers

Table 7. Area Under the Curve (AUC) for Biomarkers

Variable	AUC	p-value	95% CI (Lower–Upper)
SCC-Ag	0.522	0.867	0.223–0.822
CEA	0.518	0.894	0.218–0.817
SCC-Ag + CEA	0.580	0.548	0.275–0.886

AUC- area under the curve,
SCC-Ag- Squamous cell carcinoma antigen,
CEA- Carcinoembryonic antigen,

Discussion

This study evaluated SCC-Ag and CEA as diagnostic tools for NSCLC. SCC-Ag showed high sensitivity but very low specificity, making it unreliable as a diagnostic biomarker in this setting. SCC-Ag was elevated in most adenocarcinoma patients—an atypical pattern compared with global literature, where SCC-Ag is most associated with squamous cell carcinoma.[15] This discrepancy may reflect underlying local tumour biology or the effect of a small sample size.

CEA showed moderate sensitivity and low specificity. Many studies have demonstrated that patients with elevated serum CEA levels were more responsive to chemotherapy and targeted therapy, especially gefitinib, a tyrosine kinase inhibitor, than those with lower levels.[16] Elevated serum CEA levels were also associated with a significantly better prognosis following gefitinib treatment, in both univariate and multivariate analyses. These findings suggest that higher CEA levels may indicate a greater likelihood of responding to targeted therapy with tyrosine kinase inhibitors.[17, 18] Other studies have reported that serum CEA levels can aid in identifying histologic subtype and in detecting EGFR mutation or ALK fusion protein status in patients with lung adenocarcinoma. The solid subtype tends to exhibit higher CEA levels, whereas lepidic and some other subtypes typically show low CEA levels.[17] In this study, most patients had low serum CEA levels despite advanced stages, suggesting that many lung cancer cases in our setting may be of the lepidic subtype and EGFR-mutant. Consequently, these patients may be less likely to respond to targeted therapy with EGFR-TKIs, potentially contributing to poorer outcomes. A few patients had extremely high CEA levels and were found to be smokers, an important confounder known to elevate serum CEA levels falsely. The combined biomarker panel achieved perfect sensitivity but low specificity and a poor AUC,

indicating that although it identified nearly all NSCLC cases, it generated a high rate of false positives.

Overall, the biomarkers in this study performed poorly compared with international findings, which have shown improved diagnostic accuracy with multi-marker panels.[8, 18] This variation may reflect the small sample size, differences in histologic subtype distribution, underlying molecular profiles (e.g., EGFR and ALK status), tumour differentiation and burden and the inherent limitations of these biomarkers in terms of sensitivity and specificity.

Furthermore, recent studies have shown that combinations of serum biomarkers may improve the sensitivity of NSCLC detection, particularly when integrated with imaging modalities and molecular profiling.[12] However, the low specificity observed in this study suggests that SCC-Ag and CEA alone may not reliably distinguish malignant from benign inflammatory lung conditions commonly encountered in sub-Saharan Africa, including pulmonary tuberculosis and chronic inflammatory lung disease. Similar findings have been reported in recent Asian and African studies evaluating conventional tumour markers in resource-limited settings.[11, 19] Contemporary evidence also suggests that conventional serum biomarkers are more valuable when combined with genomic and radiologic approaches rather than being used as standalone diagnostic tools.[12, 13]

Limitations:

This study has several limitations that should be considered when interpreting the findings. First, the relatively small sample size (n = 22) reduced the study's statistical power. It may have limited the precision of estimates of diagnostic accuracy, including sensitivity, specificity, and area under the curve (AUC). Second, the study was conducted at a single tertiary institution in Northwestern Nigeria, which may limit the generalizability of the findings to other populations and healthcare settings. Regional differences in environmental exposures, smoking patterns, tumour biology, and healthcare access may influence biomarker performance. Third, the absence of a healthy control group limited the ability to establish population-specific reference values and to evaluate the discriminatory capacity of SCC-Ag and CEA between healthy individuals and patients with lung disease. Inclusion of healthy controls and patients with other respiratory conditions would have provided a more comprehensive assessment of diagnostic performance. Fourth, several benign pulmonary conditions identified among study participants, including tuberculosis, bronchiectasis, and chronic inflammatory lung diseases, are known to influence serum biomarker levels and may have contributed to the high false-positive rates observed. This is particularly relevant in sub-Saharan Africa, where infectious and inflammatory respiratory diseases remain common. Fifth, smoking status may have acted as a confounding factor, especially for CEA levels, as cigarette smoking has been associated with elevated serum CEA concentrations independent of malignancy. The limited sample size precluded adjustment for this and other potential confounders.

Conclusion

This study demonstrated that although SCC-Ag and combined SCC-Ag/CEA testing showed high sensitivity for identifying NSCLC, their poor specificity and low overall diagnostic accuracy substantially limit their clinical utility as standalone diagnostic tools. The findings underscore the challenges of relying on conventional serum biomarkers in

populations with high burdens of chronic inflammatory lung disease. Future multicentre studies involving larger cohorts, molecular characterisation, and integrated biomarker panels are needed to improve early detection of lung cancer in resource-constrained settings.

Conflict of Interest: None

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Ethical Approval:

Ethical approval was granted (EXM/PR/SURG/VOL.21/027). All participants provided informed consent.

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