Variations in Serum Steroid Hormones and Complement Levels throughout Different Stages of Lung Cancer

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***Abstract*—Lung cancer is a leading cause of cancer mortality worldwide. Steroid hormones and complement proteins may contribute to lung cancer progression and immune regulation. This case-control study enrolled 111 individuals, including 66 newly diagnosed patients with lung cancer and 45 healthy controls. Blood samples were collected from all participants between 7:00 and 9:00 AM following an overnight fast of at least 8 h before the initiation of any treatment in the lung cancer patient group. Serum steroid hormones were statistically higher in the lung cancer group than in the control group ($p = 0.0001$). In addition, the levels of serum complement C3 ($p = 0.006$) and C4 ($p < 0.0001$) in the lung cancer group were higher than those in the control group. Levels increased with disease progression. Elevated serum concentrations of pregnenolone (odds ratio [OR] = 5.12, $p = 0.036$) and progesterone (OR = 7.20, $p = 0.023$) were significantly associated with an increased risk of lung cancer. The discriminatory power for serum cortisol (area under the curve [AUC] = 0.927), progesterone (AUC = 0.948), dehydroepiandrosterone (AUC = 0.935), and complement C4 was excellent (AUC = 0.962). Increased expression of several steroid hormones and complement proteins is linked to lung cancer and continuously increases with the development of the disease. Most of the steroid hormones and complement C4 showed a favorable capacity for early diagnosis and risk prediction of lung cancer. Nevertheless, pregnenolone and progesterone are now identified as the most relevant independent biomarkers.**

Index Terms—**Biomarker, Complement system proteins, Glucocorticoids, Lung cancer, Steroid hormones.**

ARO-The Scientific Journal of Koya University
Vol. XIV, No.1 (2026), Article ID: ARO.12827. 9 pages
DOI: 10.14500/aro.12827
Received: 12 January 2026; Accepted: 24 March 2026
Regular research paper; Published: 20 June 2026
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I. Introduction

Lung cancer is still the leading cause of cancer-related death worldwide, with increased incidence and mortality rates among men (Sung, et al., 2021). The lack of specific early symptoms and limitations on population-based screening programs cause many patients to have advanced stages of their illnesses before they are diagnosed (Team, 2011). This delay in diagnosis adds to the heavy financial burden on the health care systems and exerts dramatic socioeconomic concerns on patients and their families (Mariotto, et al., 2020).

Steroid hormones are generally involved in a wide variety of physiological functions, including growth, development, energy metabolism, homeostasis, and reproduction. These compounds have powerful roles in brain development, sexual differentiation, reproductive behavior, and cognitive processes, including learning and memory (Adhya, et al., 2018). There is accumulating evidence that steroid hormones are involved in the development and progression of several cancers by modulating essential cell functions such as proliferation, apoptosis, angiogenesis, and immune regulation, among others, through diverse molecular mechanisms (Anderson and Acharya, 2022; Wang, et al., 2025). Increasingly, the lung is being viewed as an organ in which steroid hormones can generate active metabolites rather than being inactive tissue targets. Both normal and cancerous tissues in the lung express functional estrogen receptors (ERα, ERβ), progesterone receptors, and androgen receptors, indicating direct hormonal response (Rodriguez-Lara, et al., 2025). Moreover, important enzymes of steroidogenesis, such as aromatase, are expressed in lung parenchyma, leading to intrapulmonary hormone

generation and metabolism (Miki, et al., 2010). This ability to produce hormones in the tumor provides for strong autocrine and paracrine signaling within the small environment of lung tumors, which could be involved in tumor development or resistance to treatment (Wang, et al., 2025).

Key cancer-promoting pathways are activated by this local hormone synthesis. For example, proliferative pathways like MAPK/ERK and PI3K/AKT are triggered by estrogen signaling through ERβ; androgens can change the tumor environment by increasing inflammation and decreasing the immune response, whereas progesterone may have tumor-suppressive effects (Bandovkina, et al., 2019; Ishibashi, et al., 2005; Siegfried, 2014). Lung malignancies frequently display a distinct local hormonal imbalance, marked by heightened estrogenic activity relative to androgens and progestins, alongside a disordered intracrine milieu thought to facilitate tumor initiation and progression (Brown and Gervais, 2020; Stabile, et al., 2011).

Previous research on lung cancer has primarily focused on individual steroid hormones, frequently neglecting the complex interactions and balance among estrogens, androgens, progestins, and glucocorticoids, which can substantially influence tumor biology, immune regulation, and therapeutic outcomes (Becerra-Diaz, Song and Heller, 2020; Siegfried, 2014; Wang, et al., 2025). Glucocorticoids, commonly used to manage cancer-associated complications and immunotherapy-related adverse effects, add further complexity; their direct influence on lung tumor biology is not well understood and seems to be highly dependent on the specific context (Anderson and Acharya, 2022; Rodriguez-Lara, Hernandez-Martinez and Arrieta, 2018).

Glucocorticoids can exert bidirectional effects on tumorigenesis: they can inhibit tumor proliferation, modulate immunity, and facilitate the antitumor tumor microenvironment (TME). However, long-term or excessive exposure may lead to resistance and adverse treatment outcomes (Deng, et al., 2020; Musial, et al., 2021). Therefore, there is an urgent need to investigate steroid hormone-dependent signaling pathways for the pathogenesis process and the proper response of cancer patients. Rather than confining investigations to circulating hormone concentrations, future research should prioritize elucidating the intricate biology and multifaceted actions of glucocorticoid signaling, including its receptor isoforms, transcription factors, and downstream gene regulatory networks (Anderson and Acharya, 2022; Durovski, Jankovic and Prekovic, 2023; Schwarzlmueller, et al., 2025).

The complement protein system has also been considered abnormal, as reflected by the dysregulated serum complement C3 and C4 levels in patients with lung cancer. These alterations are due to local activation by the classical, lectin, or alternative pathway in the TME and systemic consumption of complement (Rutkowski, et al., 2010). The complement system has a dual role as it can induce a tumoricidal response, but chronic activation frequently skews the equation toward pro-tumorigenic actions such as immunosuppression, angiogenesis promotion, and increased metastasis (Pio, Ajona and Lambris, 2013). Consequently, depressed C3 and C4 levels frequently correlate with advanced disease and poorer prognosis, whereas specific activation fragments, such as C4, show diagnostic potential (Suliman, et al., 2021). Therefore, components of the complement system act as important biomarkers for predicting outcomes and understanding interactions between tumors and the immune system.

This study aimed to compare systemic steroid hormone and complement component (C3 and C4) profiles between individuals with lung cancer and controls and to evaluate their individual and combined associations with disease incidence. In addition, this study aimed to explore the diagnostic effectiveness of this combined biomarker panel for the early detection of lung cancer.

II. Materials And Methods

A. Study Design

This is a case-control study conducted at Hiwa's Hospital, Sulaimania, between March 2024 and May 2025. The study protocol was approved by the local ethical committee at Erbil Polytechnic University, code number (4306) on 19 February 2024, and all participants provided written informed consent.

B. Study Population

This study included 111 individuals: 66 patients with lung cancer (47 males, 19 females; mean age: 60.5 ± 11.2 years) and 45 healthy individuals who were matched to the case group for key potential confounders: age and sex (30 males, 15 females; mean age: 63.7 ± 9.2 years). Newly diagnosed patients with lung cancer, no prior surgery, chemotherapy, radiotherapy, or immunotherapy, and patients with histologically confirmed lung cancer were consecutively recruited from the Hiwa Hospital. Healthy individuals with no history of any cancer or chronic inflammatory disease were recruited from a community health screening program. Based on TNM classification, patients were categorized into clinical stages I–II and III–IV.

C. Blood Sample Collection

Peripheral venous blood (10 mL) was drawn from all participants between 7:00 and 9:00 AM after an overnight fast of at least 8 h. For the patient group, samples were collected before starting any therapeutic intervention (surgery, radiotherapy, chemotherapy, or immunotherapy). After blood was collected in a Vacutainer tube, it was allowed to clot at room temperature for 30 min, and then centrifuged at 3000 × g for 15 min. The separated serum was stored at −80°C for subsequent analysis. Serum steroid hormones were quantified using commercial enzyme-linked immunosorbent assay kits (LDN Labor Diagnostika Nord), and complement components C3 and C4 were measured via immunoturbidimetric assays (BT LAB, Bioassay Technology Laboratory). The absorbance for both assay types was determined using a BioTek 800 TS microplate reader.

D. Statistical Analysis

Statistical analyses were performed primarily using GraphPad Prism (version 10.4.2), with ROC analysis

conducted using Statistical Package for the Social Sciences (version 8). Continuous variables are reported as mean ± standard error of the mean, and categorical variables as frequencies (%). Following an assessment of normality via the Shapiro–Wilk test, inter-group differences were analyzed using one-way Analysis of Variance with Tukey's *post hoc* test. Binary logistic regression was used to compute odds ratios (ORs) for risk assessment. The diagnostic utility of the biomarkers was evaluated using ROC curve analysis. Statistical significance was defined as $p < 0.05$.

III. Results

A. Demographic Characteristics of the Study

A total of 111 individuals were enrolled in this study, including 66 patients diagnosed with lung cancer and 45 healthy controls. The mean age of the lung cancer group was 63.7 ± 9.2 years, whereas the control group had a mean age of 60.4 ± 11.2 years. The distribution of males and females was comparable between the two groups. Body mass index (BMI) categorization showed that lung cancer patients most commonly fell within the 25–30 kg/m^2 range (50%), followed by the 30–35 kg/m^2 category (27.2%). In contrast, BMI values in the control group were highest in the 20–25 kg/m^2 range (40%) and 25–30 kg/m^2 range (33.33%).

Smoking status differed markedly between the groups: 68% of lung cancer patients were heavy smokers, whereas the majority of healthy controls were never-smokers. Based on the TNM classification, lung cancer patients were further categorized into early clinical stages I–II (n = 27) and advanced stages III–IV (n = 39) as shown in Table I.

TABLE I
Baseline Characteristics of Patients with Lung Cancer and the Healthy Control Group

Variables	Control (n=45) (%)	Lung cancer (n=66) (%)	p-value
Ages	60.4±11.2	63.7±9.2	0.106
Sex			
Female	15 (33.3)	19 (28.8)	0.260
Male	30 (66.6)	47 (71.2)	
Smoking status			
Never	40 (89)	1 (1.52)	<0.0001
Current	3 (6.6)	20 (30.3)	
Heavy	2 (4.4)	45 (68.18)	
Body mass index			
20–25	18 (40)	15 (22.7)	0.015
25–30	15 (33.33)	33 (50)	
30–35	4 (8.88)	18 (27.3)	
Family history			
No	42 (93.3)	37 (56)	<0.0001
Yes	3 (6.6)	29 (44)	
Alcohol consumption			
Yes	7 (15.5)	15 (23)	0.467
No	38 (84.5)	51 (73)	
Stages			
Stage I, II		16 (24.24)	
Stage III, IV		50 (75.75)	

The values are expressed as mean±standard deviation and percentage. Statistical significant p<0.05.

B. Serum Level of Steroid Hormone Concentrations in Patients with Lung Cancer

Table II presents a comparison of serum steroid hormone levels between patients with lung cancer and healthy controls. The results reveal highly significant differences across all measured hormones. In patients with lung cancer, serum concentrations of 17-hydroxypregnenolone, pregnenolone, 17-hydroxyprogesterone, progesterone, cortisol, 11-deoxycortisol, dehydroepiandrosterone, estrogen, testosterone, and estradiol were markedly elevated compared with the control group (all $p < 0.0001$).

C. Serum Complement Concentrations in Patients with Lung Cancer

Table III compares the serum complement levels between patients with lung cancer and healthy controls. The results demonstrate a significant elevation in both complement C3 ($p = 0.006$) and complement C4 ($p < 0.0001$) compared with the control group.

D. Serum Concentration of Pregnenolone and Its Precursors across Different Stages in Lung Cancer

The serum concentrations of pregnenolone, 17-hydroxypregnenolone, progesterone, and 17-hydroxyprogesterone were substantially higher in patients with lung cancer across different stages of the disease than in those in the control group, as shown in Fig. 1. Serum pregnenolone levels were 4.96 ± 0.5 in stages I+II, whereas they were 5.44 ± 0.71 in stages III+IV, compared with the control group, which was 2.99 ± 1.03. In stages I+II, serum hydroxypregnenolone levels were 2.28 ±0.14, and stages III+IV were 3.76 ±0.26 in contrast with 1.96 ± 0.091 in the control group. Serum progesterone levels were 1.27 ± 0.21 in stages I+II and

TABLE II
Serum Steroid Hormone Concentrations in Patients with Lung Cancer and Control Group

Variables	Healthy control	Lung cancer patients	p-value
Pregnenolone (ng/L)	2.69±0.0914	5.72±0.3351	<0.0001
17-hydroxypregnenolone (ng/L)	1.61±0.1421	3.61±0.0915	<0.0001
Progesterone (ng/mL)	0.46±0.036	1.57±0.411	0.009
17-hydroxyprogesterone (ng/L)	0.688±0.0405	4.61±0.2607	<0.0001
Cortisol (ng/L)	529±42.41	1550±79.08	<0.0001
11-deoxycortisol (ng/L)	0.821±0.6077	3.709±0.08103	<0.0001
Testosterone (ng/L)	0.629±0.0307	2.79±0.0759	<0.0001
Dehydroepiandrosterone (ng/L)	6.97±0.7611	17.02±0.7843	<0.0001
Estrogen (pg/mL)	13.52±5.97	26.74±13.16	<0.0001
Estradiol (pg/L)	14.8±0.7292	28.4±2.977	<0.0001

Values are presented as mean±standard error. An independent t-test was used, and a significant difference is indicated by p<0.05

TABLE III
The Serum Complement Levels between Male and Female Lung Cancer Patients and Healthy Controls

Serum complements	Lung cancer patients	Healthy control	p-value
Complement C3 (mg/mL)	5.953±0.3103	4.691±0.3029	0.006
Complement C4 (mg/mL)	0.8319±0.0502	0.314±0.0146	<0.0001

Values are expressed as mean±standard error. An independent t-test was used, and a significant difference is indicated by p<0.05

2.28 ± 0.14 in stages III+IV compared to 0.64 ± 0.07 in the control group. Similarly, serum hydroxyprogesterone levels were 3.61 ± 0.41 in stages I+II, and 5.06 ± 0.7 in stages III+IV, in contrast to 1.98 ± 0.63 in the control group.

E. Serum Concentration of Glucocorticosteroid Hormones across Different Stages of LUNG CANCER

Fig. 2 shows a comparison of serum cortisol and deoxycortisol levels in patients with lung cancer at different stages of the disease. Patients with lung cancer exhibited substantially elevated serum cortisol and deoxycortisol levels compared to healthy controls. In stages I+II, the serum cortisol level was 1188.80 ± 41.7, whereas in stages III+IV, it was 1492.87 ± 78.08, in comparison with healthy controls, which were 456 ± 40.72. Similarly, deoxycortisol levels in stages I+II were 3.32 ± 0.3041, whereas in stages III+IV they were 3.941 ± 0.411, in comparison with healthy controls, which were 0.751 ± 1.301.

F. Serum Concentrations of Androgen Hormones across Different Stages of Lung Cancer

Fig. 3 shows that patients with lung cancer exhibited substantially elevated serum levels of testosterone and

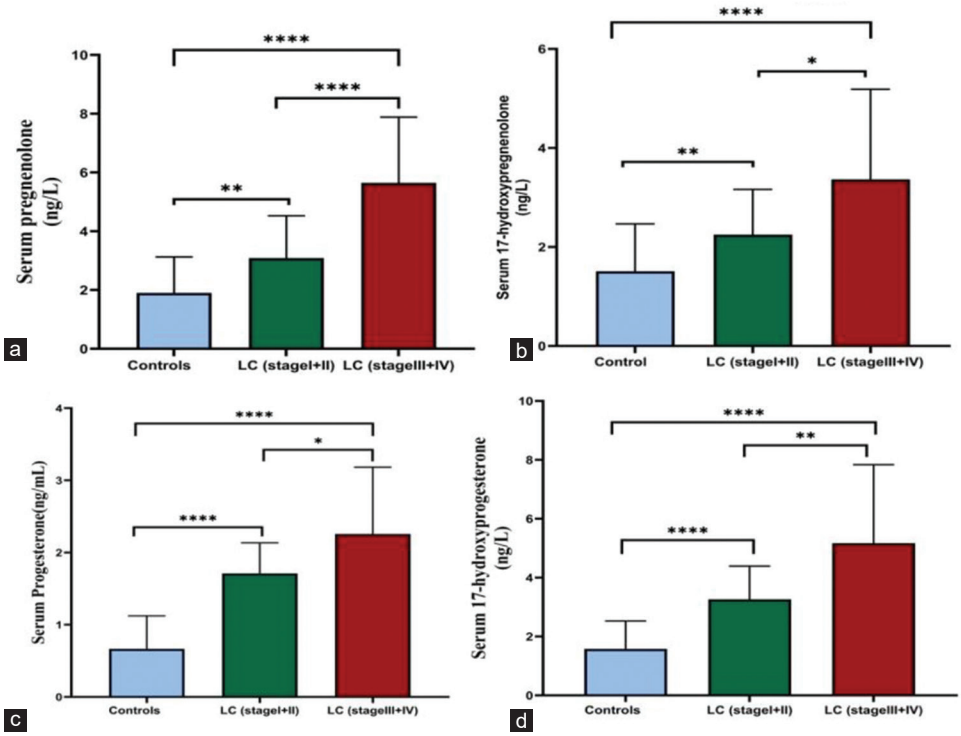

Fig. 1. Comparison of serum (a) pregnenolone, (b) 17-hydroxypregnenolone, (c) progesterone, and (d) 17-hydroxyprogesterone levels between patients with lung cancer and the healthy control group. One-way Analysis of Variance multiple comparison followed by Tukey's test was used. Indicates statistically significant *p<0.05, **p=0.001, ***p=0.0001, ****p<0.0001.

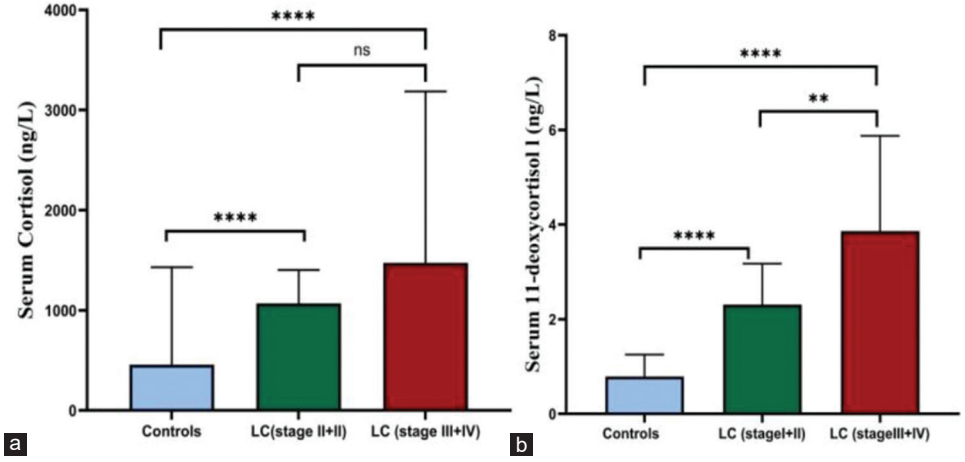

Fig. 2. Comparison of serum (a) cortisol and (b) deoxycortisol levels between patients with lung cancer and the healthy control group. One-way Analysis of Variance multiple comparison followed by Tukey's test was used. Indicates statistically significant ns= non-significant, **p=0.001, ***p=0.0001, ****p<0.0001.

dehydroepiandrosterone (DHEA) compared to healthy controls, with significant differences across various stages. In stages I+II, serum testosterone levels were 17.52 ± 0.739 pg/mL, whereas in stages III+IV, they were 20.11 ± 9.24 pg/mL, in contrast to 15.11 ± 3.96 pg/mL in healthy individuals. Likewise, serum DHEA levels were 16.25 ± 0.503 pg/mL in stages I+II and 20.13 ± 0.784 pg/mL in stages III+IV, compared with 7.03 ± 0.661 pg/mL in the control group.

G. Serum Estrogen Levels in Patients with Lung Cancer at Different Clinical Stages

As illustrated in Fig. 4, serum levels of estrogen and estradiol were markedly elevated in patients with lung cancer compared to healthy controls, with significant differences observed across clinical stages. Specifically, serum estrogen levels were 25.17 ± 1.48 pg/mL in stage I+II and 27.62 ± 2.27 pg/mL in stage III+IV, compared to 15.32 ± 5.47 pg/mL in healthy individuals. Similarly, serum estradiol levels were significantly higher in patients, measuring 37.58 ± 6.03 pg/mL in stage I+II and 49.30 ± 5.12 pg/mL in stage III+IV, relative to 27.40 ± 2.31 pg/mL in controls.

H. Serum Concentration of Complement 3 and 4 across Different Stages of Lung Cancer

As shown in Fig. 5, patients with lung cancer exhibited significantly elevated serum complement C3and C4 compared to healthy controls across different stages of the disease. In stages I+II, the serum complement C3 level was 5.027 ± 0.3677 mg/mL, whereas in stages III + IV, it was 7.322 ± 0.4662 mg/mL, in contrast to 4.097 ± 0.291 mg/mL in the control group. Serum complement C4 levels were 6.3941 ± 0.4245 mg/mL in stages I+II and 9.504 ± 1.475 mg/mL in stages III+IV, compared with 0.396 ± 0.0393 mg/mL in the control group.

I. Logistic Regression Model for Serum Steroid Concentration for Lung Cancer Risk

In the multivariable logistic regression analysis assessing the association between serum steroid levels and lung cancer, age, sex, smoking status, and BMI were included as covariates. After adjustment, steroid concentrations showed significant independent predictors of lung cancer risk. Serum pregnenolone and progesterone exhibited the strongest associations with lung cancer risk, demonstrating

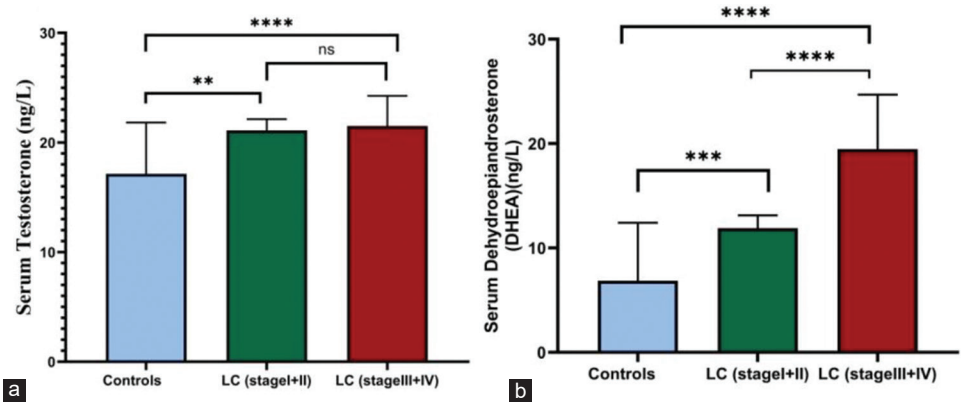

Fig. 3. Comparison of serum (a) testosterone and (b) dehydroepiandrosterone levels between patients with lung cancer and the healthy control group. One-way Analysis of Variance multiple comparison followed by Tukey's test was used. Indicates statistically significant **p=0.001, ***p=0.0001, ****p<0.0001.

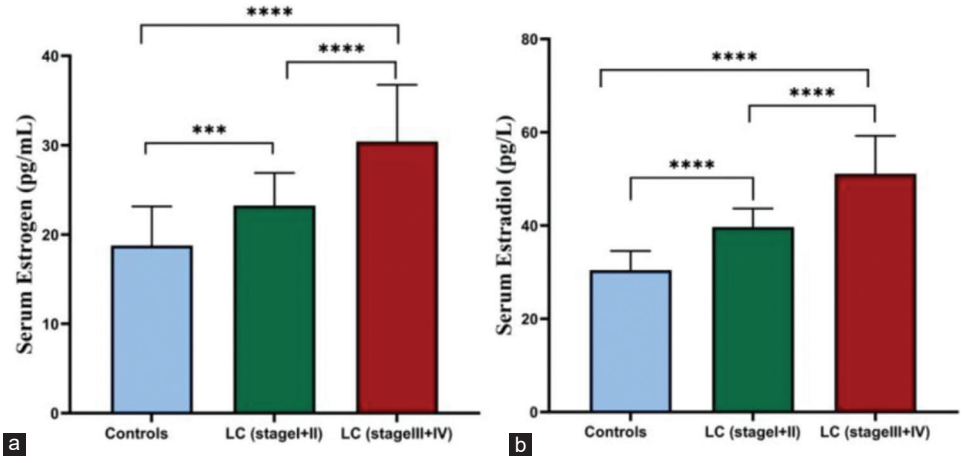

Fig. 4. Comparison of serum estrogen and estradiol levels between patients with lung cancer and the healthy control group. One-way Analysis of Variance multiple comparison followed by Tukey's test was used. Indicates statistically significant **p=0.001, ***p=0.0001, ****p<0.0001.

robust and independent effects (adjusted OR = 5.12, p = 0.036; and adjusted OR = 7.2, p = 0.023, respectively). Elevated concentrations of DHEA, 17-hydroxyprogesterone, deoxycortisol, cortisol, estrogen, estradiol, and complement C4 were significantly associated with moderately increased lung cancer risk in the adjusted analyses. In contrast, serum hydroxypregnenolone, testosterone, and complement C3 levels showed no significant associations after adjustment, indicating limited predictive value for lung cancer in this cohort, as shown in Table IV.

J. Receiver Operating Characteristic (ROC) Analysis of Serum Steroid Concentrations for Lung Cancer

ROC analysis revealed that the diagnostic performance of steroid biomarkers differed substantially in lung cancer. Serum concentration of DHEA (area under the curve [AUC] = 0.935), cortisol (AUC = 0.927), progesterone (AUC = 0.948), and complement C4 (AUC = 0.962) exhibited excellent discriminatory power. Whereas serum concentration of deoxycortisol (AUC = 0.856), estradiol (AUC = 0.828), 17-hydroxyprogesterone (AUC = 0.836), and pregnenolone (AUC = 0.863) showed very good accuracy. The serum concentrations of testosterone (AUC = 0.638), 17-hydroxypregnenolone (AUC = 0.680), and complement C3 (AUC = 0.699) reveal a moderate diagnostic value. These findings suggest that specific steroid hormones may serve as valuable biomarkers for lung cancer detection, as shown in Table V.

IV. Discussion

The present study demonstrated a significant elevation in serum steroid hormone concentrations and complement proteins in newly diagnosed patients with lung cancer compared to those in the control group. Furthermore, higher variability in steroid hormone concentrations and complement proteins was correlated with advanced lung cancer stages and increased disease severity. Serum steroid hormone and complement protein elevations are linked to an increased risk of lung cancer and have the potential to serve as validated biomarkers for the detection of the disease at an early stage, assessment of its severity, and risk stratification. The alterations in steroid hormone and complement levels observed in lung cancer patients may indicate greater disruptions to steroidogenesis, potentially induced by tumor-associated stress and immune system dysregulation. These

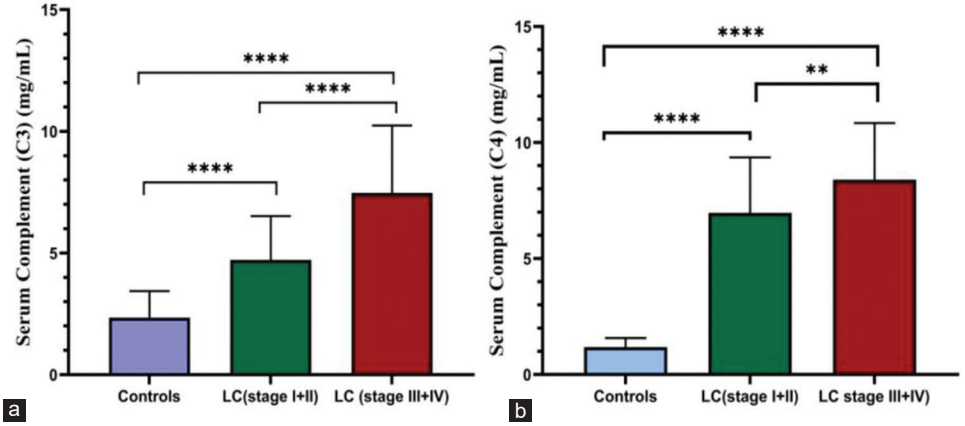

Fig. 5. Comparison of serum (a) complement C3 and (b) complement C4 levels between patients with lung cancer and the healthy control group. One-way Analysis of Variance multiple comparisons followed by Tukey's test was used. Indicates statistically significant **p=0.001, ***p=0.0001, ****p<0.0001.

TABLE IV
Multivariable Analysis of Crude and Adjusted Odds Ratios for the Association between Steroid Concentrations and Lung Cancer Risk

Variable	OR (crude)	95% CI	P-value	OR (adjusted)	95% CI	p-value
Pregnenolone (ng/mL)	2.25	1.63–3.10	0.001	5.125	1.11–9.04	0.036
17-Hydroxypregnenolone (ng/mL)	1.56	1.17–2.08	0.003	1.29	0.588–2.86	0.524
Progesterone (ng/mL)	3.7	1.81–7.89	<0.0001	7.2	1.33–39.5	0.023
17-Hydroxyprogesterone (ng/mL)	1.6	1.27–2.03	<0.0001	1.52	1.02–2.26	0.036
Cortisol (ng/mL)	1.01	1.02–1.03	<0.0001	1.05	1.00–1.02	0.034
11-Deoxycortisol (ng/mL)	3.84	2.11–7.00	0.001	2.89	1.31–6.37	0.008
Testosterone (ng/mL)	1.03	0.94–1.12	0.465	1.073	0.92–1.25	0.352
Dehydroepiandrosterone (ng/mL)	1.36	1.21–1.53	<0.0001	1.6	1.06–2.44	0.024
Estrogen (pg/mL)	1.14	1.07–1.21	<0.0001	1.23	1.06– 1.43	0.007
Estradiol (pg/mL)	1.07	1.04–1.13	<0.0001	1.31	1.047–1.22	0.002
Complement C3 (mg/mL)	1.26	1.12–2.43	<0.0001	1.22	0.923–1.68	0.144
Complement C4 (mg/mL)	6.41	2.97–13.84	0.001	2.96	1.54–5.70	0.001

OR: Odds ratio, CI: Confidence interval. Statistically significant p<0.05

TABLE V
Receiver Operating Characteristic Analysis of Steroid Concentrations as Biomarkers for Lung Cancer

Variables	AUC	95%CI	p-value	Sensitivity	Specificity
Pregnenolone (ng/mL)	0.863	0.798–0.929	0.0001	95.5	53.3
17-Hydroxypregnenolone (ng/mL)	0.680	0.581–0.780	0.0001	83.3	66.7
Progesterone (ng/mL)	0.948	0.913–0.983	0.0001	97.3	45.5
17-hydroxyprogesterone (ng/mL)	0.836	0.754–0.917	0.0001	93.9	57.8
Cortisol (ng/mL)	0.927	0.863–0.992	0.0001	95.5	53.3
11-Deoxycortisol (ng/mL)	0.856	0.785–0.927	0.0001	95.5	57.8
Testosterone (ng/mL)	0.638	0.535–0.741	0.014	81.8	68.9
Dehydroepiandrosterone (ng/mL)	0.935	0.883–0.986	0.0001	97	53.3
Estrogen (pg/mL)	0.876	0.808–0.944	0.0001	90.9	57.8
Estradiol (pg/mL)	0.828	0.746–0.909	0.0001	87.9	66.7
Complement C3 (mg/mL)	0.699	0.571–0.827	0.0001	97.5	33.3
Complement C4 (mg/mL)	0.962	0.931–0.993	0.0001	98.5	33.3

AUC: Area under curve, CI: Confidence interval. Statistically significant $p<0.05$

steroid hormones may shift in response to increased metabolic and immunological demands within the TME. Such changes may also arise from disrupted steroidogenic enzyme activity or paraneoplastic effects, particularly in aggressive lung cancer subtypes. Although direct evidence remains limited, these findings suggest that steroid hormones could serve as sensitive indicators of hypothalamic–pituitary–adrenal (HPA) axis dysregulation and emerging biomarkers for lung cancer progression and disease monitoring. Higher levels of pregnenolone, progesterone, hydroxyprogesterone, and hydroxypregnenolone observed in patients with lung cancer may result from altered local steroid hormone metabolism and receptor activity within tumors and influence tumor growth and progression (Bandovkina, et al., 2019; Wang, et al., 2025). These findings are consistent with numerous studies (Cernera, et al., 2022).

The current study reveals increased serum concentration of glucocorticosteroid hormones (cortisol and deoxycortisol) in patients with lung cancer compared to healthy controls. A study by Sharma, et al. reported that increased cortisol levels in lung cancer patients are probably a result of the activation of the HPA axis in response to inflammation and stress related to the tumor (Sharma, et al., 2014).

In the current study, we observed increased concentrations of testosterone and DHEA in lung cancer patients compared to the control group, reflecting their role in hormone signaling pathways that influence tumor growth and progression. These effects are modified by factors such as age and smoking status, which also impact lung cancer risk (Buendía-González and Legorreta-Herrera, 2022; Ørsted, Nordestgaard and Bojesen, 2014; Zhang, et al., 2024). A study has identified that the reduced serum testosterone levels observed in patients with lung cancer may be attributed to the heightened activity of aromatase, a rate-limiting enzyme responsible for the conversion of androgens into estrogens within lung tissues (Wu et al., 2019). This difference in testosterone levels is probably due to differences in disease staging and methodological variations. Although elevated testosterone levels are expected in advanced cancer due to systemic inflammation and cachexia, low disease stages or tumor types can be characterized by elevated androgens as a pro-proliferative or compensatory effect. Moreover, the differences in patient age and sampling time used in the studies also make these results conflicting.

Estrogen is a key steroid hormone implicated in the development and progression of several malignancies. The present research revealed high levels of estrogen in the serum of patients diagnosed with lung cancer. These results align with the previous studies (Bai, et al., 2019; Chen, et al., 2017; Rodriguez-Lara, Hernandez-Martinez and Arrieta, 2018), which show that high levels of serum estrogens are associated with a shorter lifespan in patients with lung cancer and can be used to detect and manage the disease at an early stage.

The present study revealed a significant positive association between increased serum concentrations of pregnenolone and progesterone and an increased risk of lung cancer. These findings add to the growing literature on the complex and multifaceted roles of sex steroid hormones in pulmonary carcinogenesis. Our findings show that the contribution of upstream pregnenolone and progesterone might be significant in determining the risk of lung cancer, even though previous studies have given much attention to estrogen and testosterone in the pathogenesis of lung cancer. Steroid hormones have a complicated effect on inflammation and immunological activity, which are critical in the development and progression. (Smith, et al., 2025) found that progesterone and its active metabolites change the way immune cells work. This includes the behavior of tumor-associated macrophages, regulatory T lymphocytes, and natural killer cells. These changes can shape the TME and impact cancer risk.

Chronic inflammation represents a significant risk factor for the development of lung cancer, especially in individuals with a history of cigarette smoking or chronic obstructive pulmonary disease. There may be a mechanistic connection between excessive progesterone and pregnenolone and a higher risk of cancer if they lead to prolonged inflammatory signaling or compromised immune surveillance (King, 2015).

Elevated serum levels of cortisol, 17-hydroxyprogesterone, estrogen, DHEA, deoxycortisol, and estradiol suggested a strong correlation with a higher incidence of lung cancer. This association suggested that hormonal and immunological factors may contribute to tumorigenesis or disease progression in the pulmonary system (Feng, et al., 2025). Estrogen and estradiol, sex hormones, demonstrated

the capacity to increase the proliferation and invasiveness of pulmonary carcinoma cells by inactivating factors that facilitate tumor cell growth and neovascularization. Similarly, adrenal hormones such as cortisol and DHEA may influence tumor development and progression by participating in immune modulation and inflammation (Chakraborty, et al., 2010). The findings were consistent with those reported in prior research (Feng, et al., 2025; Fuentes, Silva Rodriguez and Silveyra, 2021; Nuvoli, et al., 2024; Pelizzo, et al., 2024; Siegfried and Stabile, 2014; Zhang, et al., 2024). The findings regarding serum complement C4 levels indicated a moderate correlation with an intermediate risk of lung cancer. This association may be attributed to immune dysregulation, which potentially facilitates tumor progression.

Complement protein C4 is a part of the classical and lectin pathway that regulates the opsonization and recruitment of immune cells within the inflammatory tumor microenvironment, and consequently impacts cancer susceptibility. This result aligned with prior studies (Ajona, Okrój and Pajares, 2017; Ajona, et al., 2021; Li, et al., 2019) that imply dysregulation of the immune and hormonal pathways has the potential to influence disease progression and prognosis and elevated cancer susceptibility. This study exhibited that various steroid hormones, such as DHEA, cortisol, progesterone, and supplementary C4, have high levels of diagnostic accuracy in patients with lung cancer. The hormones with high discriminatory performance were deoxycortisol, estradiol, 17-hydroxypregnenolone, pregnenolone, and the hormones with moderate discriminatory performance were testosterone, 17-hydroxypregnenolone, and complement C3. These results are greater than those of previous studies, where AUC measures of individual steroid hormones remained relatively constant at 0.70-85 (Siegfried and Stabile, 2014; Wu, et al., 2024).

The enhanced diagnostic performance observed in the study could reflect notable steroidogenesis dysregulation that is associated with lung tumorigenesis. Increased expression of key steroidogenic enzymes, such as CYP17A1, CYP11B1, and 3β-HSD, has been detected in lung cancer cells, thereby accelerating synthesis of glucocorticoids and androgen precursors (Drzewiecka, et al., 2015). In addition, persistent inflammation in the TME activates the HPA axis, resulting in sustained cortisol elevation and blockade of antitumor immune response (Kanter, et al., 2024). Estrogen signaling can further promote disease progression through an increase in intratumoral aromatase activity and ER-mediated proliferative pathways (Hsu, Chu and Koa, 2017; Verma, Miki and Sasano, 2011). These changes result in the formation of a distinct steroidogenic pattern, which provides higher accuracy in diagnostics when hormonal analyses are combined as a unified biomarker panel, rather than as independent individual parameters. The findings are highly indicative of the fact that multidimensional profiles of steroids may be utilized as diagnostic biomarkers of lung cancer; however, further studies are required in larger and more heterogeneous populations before they can be applied in the clinic. This study included several limitations. The small sample size from a single institution limits the generalizability of our findings to diverse populations. The fact that samples were mostly collected in the morning is a significant drawback of this study; the lack of evening data makes it impossible to fully evaluate the diurnal fluctuation of cortisol and other steroid hormones. The menopausal status of subjects was insufficiently described, and only total hormone amounts were measured, ignoring binding proteins such as sex hormone-binding globulin or albumin; thus, knowledge of biologically active fractions is restricted. In addition, molecular mechanisms underlying steroidogenic changes in lung cancer have not been studied, and inflammatory profiling has been limited to complement factors. Further research is required to investigate the impact of cytokines and anti-inflammatory mediator levels on immune balance and to understand the mechanisms by which hormones modulate the immune response.

V. Conclusion

In this study, newly diagnosed patients with lung cancer exhibited a significant elevation in the serum concentrations of various steroid hormones and complement proteins; increased levels were significantly correlated with advanced stages of lung cancer. Serum levels of pregnenolone and progesterone were identified as independent risk factors for lung cancer. Furthermore, most of the steroid hormones, except testosterone, and complement C4, show promising diagnostic potential in early diagnosis and risk prediction for lung cancer.

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