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Endogenous oxidative stress, advanced glycation end products and morphological particularisation of red blood corpuscles in patients with non-small-cell lung carcinoma

Pranav Menon[1], Asim Badar[3], Samreen Zaheer[2], Mohammad Akram[2], Khursheed Alam[1], Priya Philip Kadavil[1] & Zarina Arif[1]*

[1]Department of Biochemistry, Jawaharlal Nehru Medical College; & [2]Department of Radiotherapy, Faculty of Medicine, Aligarh Muslim University, Aligarh-202 002, Uttar Pradesh, India

[3]Noida International Institute of Medical Sciences, Greater Noida-203 201, Uttar Pradesh, India

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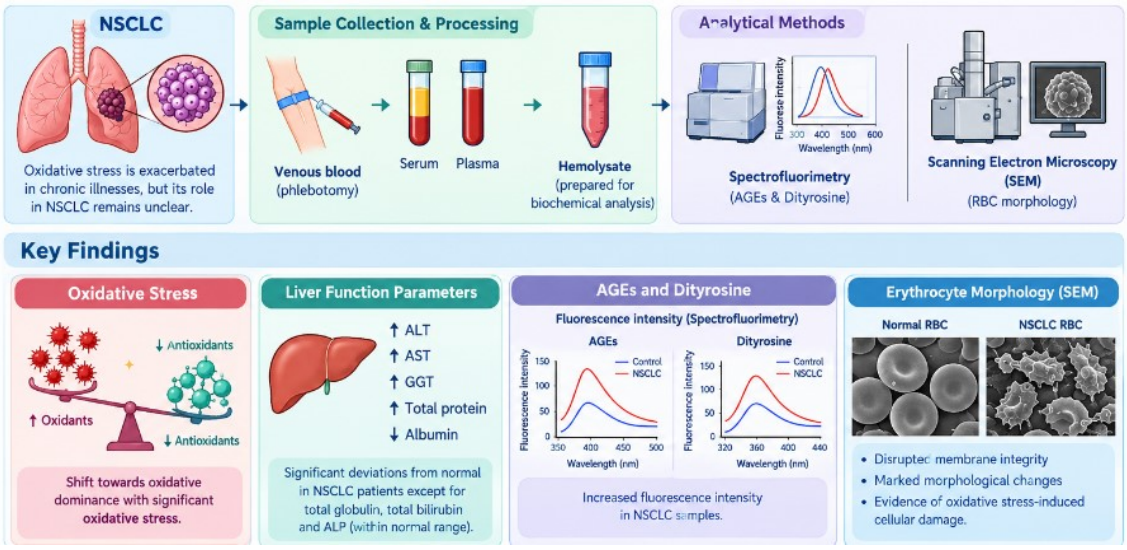
Oxidative stress is known to be exacerbated in chronic illnesses, yet its role and underlying mechanisms in non-small cell lung cancer (NSCLC) remain unclear. Venous blood samples were collected via phlebotomy and processed to separate serum and plasma. Hemolysate was prepared for biochemical analysis across the collected samples. Additionally, scanning electron microscopy (SEM) was utilized to assess the morphological characteristics of red blood cells (RBCs). A shift in the oxidant-antioxidant equilibrium towards oxidative dominance was evident, with significant oxidative stress detected in the samples. Liver function parameters portrayed consequential deflections from normal in the NSCLC population except for the total globulin, total bilirubin and ALP. Advanced glycation end products and dityrosine showcased an elevation in fluorescence intensity. SEM analysis revealed marked morphological changes in erythrocytes, including disrupted membrane integrity, highlighting oxidative stress-induced cellular damage. NSCLC patients experienced a significant decline in both biochemical and morphological protective variables thus rendering disease progression.

Keywords: Advanced glycation end-products, Erythrocytes, Human serum albumin, Non-small cell carcinoma, Oxidative stress

Lung carcinoma, a life threatening illness causing significant morbidity and mortality in humans has been under the limelight for the past century. It accounts for 12.2 percent of the newly diagnosed cases of cancer and a mind staggering 19 percent of the disease specific mortality globally[1,2]. Eighty five percent among the disease specific group are non-small cell lung cancers (NSCLC) and the remaining fifteen percent comprises the small cell lung cancer (SCLC). Although the illness has a multifaceted etiopathology, smoking remains a detrimental factor in the onset and progression of the disease. Studies have shown sidestream smoke as an equally life threatening entity compared to mainstream smoke, thus making not only active but also passive smoking a harbinger of the disease[3,4]. Notwithstanding the fact that, link between cigarette smoking and redox imbalance in lung cancer has been extensively studied and is widely known, factors like endogenous metabolic disturbances of glucose and lipids may also contribute to systemic oxidative stress in these patients[5]. The tumor microenvironment (TME) thus created acts as a plowed, manure rich soil for the insidious onset of inflammation and its progression into cellular atypia.

Inflammation and carcinogenesis promotes the production of reactive species (RS), inevitably leading to a state of high oxidative stress. RS can be classified into two main categories: reactive radicals and non-radical species. Among the radicals are superoxide, oxygen radicals, hydroxyl radicals, alkoxy radicals, peroxyl radicals, nitric oxide, and nitrogen dioxide. Non-radical species include hydrogen peroxide, hypochlorous acid, hypobromous acid, ozone, singlet oxygen, and peroxynitrite[6]. Reactive species have detrimental effects on the cellular macromolecules like DNA, RNA, Proteins and Fatty acids, thus affecting its normal biochemical cascade. This in turn leads to aberrant cellular proliferation, questions membrane integrity and seeds both enzymatic and non-enzymatic post translational modification of proteins[7]. Protein carbonyl detected in serum acts as a marker of protein oxidation[8]. Whereas

*Correspondence:
E-mail: zarif66@gmail.com



Graphical abstract

malondialdehyde (MDA) functions both as a marker of lipid peroxidation as well as an oxidant. Lipid peroxidation and modification of transmembrane protein channels can directly affect the membrane integrity of red blood corpuscles, predeceased by anisopoikilocytosis and hemolysis[9-11]. Excess oxidative stress has also been postulated to downregulate cytochrome B5 reductase, thus impeding the convection of methemoglobin back to hemoglobin causing left shift of the oxygen dissociation curve and enhancing tissue hypoxia[12].

The human body has a delicate interplay of oxidants and antioxidants. The only free thiol (-SH) group on cys34 in human serum albumin (HSA) functions as a major serum antioxidant, presuming 70 percent of this function[13]. Oxidation of the thiol group (-SH) to disulphide moiety (S-S) impedes the normal homeostasis thus affecting the antioxidant capacity of the serum. Ascorbic acid (Vitamin C) with glutathione and alpha tocopherol (vitamine E), a major constituent of redox coupling reaction and a free radical scavenger acts as a major non-enzymatic antioxidant enabling the conversion of singlet oxygen and hydrogen peroxide to water[14,15]. The whole non-enzymatic antioxidant strength of the serum can be measured using its ability to reduce ferric ion to ferrous state in-vitro alias Ferric Reducing Antioxidant Power (FRAP).

Particulars with regards to how oxidative stress markers like methemoglobin, protein carbonyl and MDA, and antioxidants including serum free thiol (-SH), ascorbic acid and antioxidant capacity of serum (AOC) are affected by NSCLC, are slender. This study investigates the percentage hemolysis, methemoglobin, protein carbonyl, dityrosine, advanced glycation end products (AGEs) and MDA along with serum free thiol (-SH), ascorbic acid, AOC of serum and a few other enzymatic parameters, unexplored like aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP). The research also tries to analyze the effect of oxidative stress on the morphology of red blood corpuscles. Using the data, we sought to determine the role of endogenous oxidative stress in lung carcinoma.

Materials and Methods

Study design

This study was performed in accordance with the declaration of Helsinki as revised in 2013. The institutional ethics committee approved the study protocol and informed consent was obtained from all the subjects. This study was performed at the Department of Biochemistry and Radiation Oncology at Jawaharlal Nehru Medical College, AMU, Aligarh. The study included 30 patients with freshly diagnosed lung carcinoma and 30 healthy subjects marking a total sample size of 60.

The clinical diagnosis of lung carcinoma was confirmed by histopathological examination of the biopsy specimen. The control subjects were asymptomatic and their physical examination results were normal. The enrolled patients and controls did not receive antioxidant vitamin supplementation such as vitamin E and C. Patients with an acute systemic

infection and other comorbidities on regular medications were excluded from the study.

Blood sample collection

Blood samples were obtained as soon as the patient was confirmed for NSCLC. A total of 10 mL blood was obtained and then segregated. Five millilitres of blood was collected into each of two separate vacutainer tubes, one containing a clot activator and the other containing EDTA, for the respective analyses. The blood samples were stored at 4°C immediately after collection. After a brief standing period, the samples were centrifuged at 5000 g for 10 minutes and the serum and plasma were separated and stored in aliquots. The biological fluids were stored at -20°C until the biochemical parameters were assessed.

Computation of total protein, human serum albumin and A: G ratio

Total protein was quantified using Lowry's method and HSA using BCG dye binding method[16,17]. Globulin concentration was calculated by subtracting the serum albumin concentration from the total serum protein concentration. The albumin-to-globulin (A:G) ratio was subsequently calculated by dividing the serum albumin concentration by the globulin concentration.

Determination of hepatic enzymatic parameters and total serum bilirubin

AST and ALT activity were determined using the Reitman and Frankel method[18]. ALP activity was deciphered using the King and Kind method[19] and total bilirubin concentration in the sera determined with the help of Jendrassik-Grof method[20].

Assessment of Methemoglobin and Percentage Haemolysis

The methemoglobin was accessed using a spectrophotometric approach. Hemolysate was prepared using the red blood cells in the EDTAted vacutainers. Serial readings were taken at 540, 575 and 630 nm, respectively and the quantity of methemoglobin was calculated. For deciphering percentage hemolysis, washed RBCs were suspended in PBS (20mM, pH 7.4) and in distilled water, respectively. The latter was used as a control. Readings were taken at 540 nm and the percentage hemolysis was calculated.

Measurement of antioxidants status in serum

Vitamin C, free thiol (- SH) and Ferric reducing antioxidant power (FRAP) were performed to analyze the antioxidant status of the serum. The Aye Kyaw method was used for the estimation of ascorbic acid[21]. Free thiol content was calculated using Sedlak and Lindsay method[22]. FRAP test, a technique developed by Benzie and Strain was used to judge the total antioxidant status of the serum[23].

Analysis of oxidative markers in serum

To determine the oxidative stress, pro oxidative stress markers like protein carbonyl and malondialdehyde (MDA) were evaluated. Protein carbonyl was worked out using Levine et al method[24] and MDA was deciphered using the Buege and Aust method[25].

Spectrofluorometric assessment of dityrosine and Advanced Glycation End Products (AGE's)

A spectrofluorometer was used to analyze both dityrosine and AGEs in the given serum sample. The excitation wavelength for dityrosine was set at 325 nm and the emission between 330 and 440 nm. Whereas for the AGEs the sample was excited at 370 nm and emission was between 375 to 500 nm. The data of both the groups were scrutinized, the average values were obtained and juxtaposing graphs were plotted as in accordance with the above values. With the peak values, percentage increase in fluorescence intensity (FI) was calculated.

$$\% \text{ Increase in FI} = \frac{(FI\ patient - F\ \ control)}{FI\ patient}$$

Scanning electron microscopy

Patient and control erythrocytes were washed with PBS (10 mM, pH 7.4) and fixed with 2.5 % glutaraldehyde for 1 hour at room temperature. The cells were separated and washed again with PBS. The cells were then washed and dried at 37 degree celsius with graded ethanol (50%, 70%, 90%,100%). The samples were air dried and coated with a gold-palladium layer and examined under the scanning electron microscope (JEOL, Japan, JSM 6510LV).

Statistical analysis

All the experiments were done in triplicates. The results are presented as mean ± SD. The data was analyzed using google sheets. Parameters between groups were compared using Student's t-test and a p-value < 0.05 was considered statistically significant.

Results

Demographic and Anthropometric parameters

The demographic and clinical data for both patient and control group are shown in (Table 1). No

statistically significant correlation was found between the two groups with respect to age, sex and height (P> 0.05; Table 1). The 2 females out of the 30 in both patient and control population marking an exception, all the other subjects proved to be active smokers. But, none of them consumed alcohol. Both weight and BMI were found to be in a notably lower range in the patient group compared to the controls (P< 0.05; Table 1).

Enzymatic and Non-Enzymatic liver function variables

The parameters of liver function are summarized in (Table 2), every single factor except total bilirubin, globulin and alkaline phosphatase expressed statistical significance (P< 0.05). Total protein, albumin and the AST:ALT ratio were markedly diminished in the patient population (P< 0.001). Although A: G ratio reversal was inconspicuous, the patient population displayed a mild pruning in the above variable (P< 0.05). Both AST and ALT manifested a momentous upsurge in the patient bracket (P< 0.001).

Oxidative markers and antioxidant status of serum.

Considering the pro oxidative markers in (Table 3), with an exception of methemoglobin (P> 0.05) all other variables proved a factor of significance. Percentage hemolysis, MDA and protein carbonyl showed a blatant upsurge in the patient population as compared to the control (P< 0.001). Antioxidants, that is free thiol and ascorbic acid, were remarkably lowered in the patient population (P< 0.001). The FRAP, manifesting as the total non-enzymatic antioxidant property of sera, was also found to be significantly diminished in the patient bracket (P< 0.001).

Advanced glycation end products and dityrosine.

Both Figures 1a and b extrapolates the graphical representation of dityrosine and AGEs. Dityrosine as well as AGEs showed a marked upsurge in the patient group with a considerable elevation of 86.34 and 69.65 percent, respectively (P< 0.001).

Morphological interpretation of erythrocyte membrane integrity

The Figure 2 represents the SEM examination of erythrocyte morphology. A portrays the patient RBCs

Table 1 — Demographic and anthropometric data of study participants

Parameters	Patients	Controls	P Value
Sex (Male/ Female)	28/2	28/2	1.00
Age (Years)	55 ± 12.16	50 ± 9.56	0.264
Height (meters)	1.65 ± 0.10	1.67 ± 0.06	0.846
Weight (kg)	57.84 ± 8.47	69.88 ± 8.69	<0.05**
BMI	19.55 ± 1.85	22.26 ± 1.45	<0.05**
Smokers	28	28	1.00
Alcoholics	0	0	1.00

Values are expressed as mean ± SD or number of subjects

Table 2 — Parameters of Liver function

Parameters	Patients	Controls	P Value
T. Protein (g/dL)	5.82 ± 0.69	7.65 ± 0.46	<0.001*
Albumin (g/dL)	3.38 ± 0.42	5.03 ± 0.28	<0.001*
Globulin (g/dL)	2.43 ± 0.59	2.62 ± 0.47	0.067
A:G Ratio	1.49 ± 0.52	1.92 ± 0.35	<0.05**
AST (U/L)	58.15 ± 12.51	14.51 ± 1.78	<0.001*
ALT (U/L)	68.96 ± 11.25	14.53 ± 2.56	<0.001*
AST:ALT Ratio	O.85 ± 0.17	1.05 ± 0.20	<0.001*
ALP (IU/L)	9.61 ± 2.36	9.18 ± 2.99	0.841
T. Bilirubin (mg/dL)	0.76 ± 0.12	0.77 ± 0.11	0.588

Values are expressed as mean ± SD. T. Protein = Total protein; A:G Ratio = Albumin:Globulin Ratio; AST = Aspartate Aminotransferase; ALT = Alanine Aminotransferase; ALP = Alkaline Phosphatase; T. Bilirubin = Total Bilirubin

Table 3 — Values of oxidative markers and Antioxidants

Parameters	Patients	Controls	P Value
Methemoglobin (μmol/L)	4.47 ± 0.07	4.43 ± 0.13	0.843
Percentage hemolysis (%)	54.68 ± 11.68	11.67 ± 2.93	<0.001*
MDA (nmol/mL)	16.20 ± 6.45	3.38 ± 0.95	<0.001*
Protein carbonyl (nmol/mg)	1.14 ± 0.78	0.23 ± 0.01	<0.001*
Thiol -SH (μM)	342.74 ± 53.76	477.97 ± 42.84	<0.001*
Ascorbic acid (mg/L)	6.61 ± 0.82	11.79 ± 1.93	<0.001*
FRAP (μM)	119.96 ± 38.60	461.73 ± 134.72	<0.001*

Values are expressed as mean ± SD. MDA = Malondialdehyde; -SH = Free Thiol; FRAP = Ferric Reducing Antioxidant Power

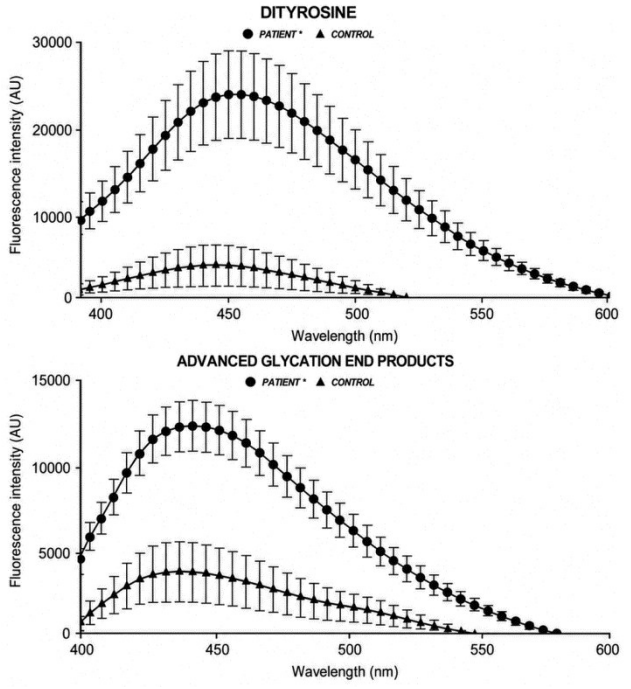


Fig. 1 — Spectro-fluoroscopic assessment of (a) Dityrosine; and (b) AGE's in sera of patient and control brackets. The spectra are the mean ± SD of 30 determinations

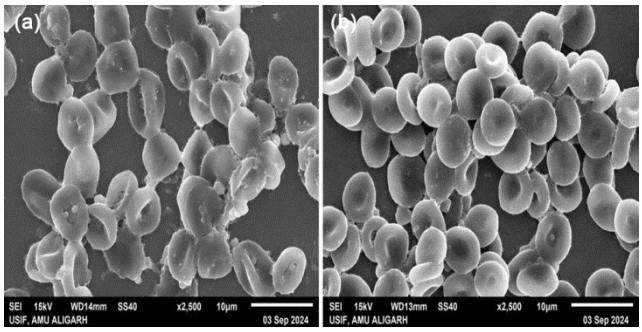


Fig. 2 — SEM of RBCs under 2500 X with respect to patient and control representing significant morphological variations with respect to the patient sample

whereas B represents the control RBCs. With regard to the control the patients' red cells reveal, membrane alterations like anisopoikilocytosis, ballooning of cells and loss of its normal morphological biconcave contour. Lysed RBCs are also visible in the patient sample.

Discussion

Reactive species have been implicated in the pathogenesis of numerous chronic diseases, including NSCLC. Prior research has established a correlation between elevated levels of RS and an upregulation in tumor cell migration, invasion, and its metastatic potential[26,27]. Notably, cancer cells often exhibit both RS production and sensitivity to oxidative stress in an exponential fashion[28]. Given these observations, antioxidant enzymes and molecules have emerged as promising therapeutic targets in the management of malignant diseases[29]. While the role of the oxidative system in lung carcinoma has been the subject of investigation, the existing data remains limited and inconclusive. Our study provides novel insights into the oxidative stress profile of patients with neoplasia lung. We observed an elevation in oxidative stress markers and reduced antioxidant levels. This comprehensive analysis, examining multiple parameters, contributes to the limited existing data in this area. Taking anthropometric data (Table 1), that is weight and BMI into consideration, the study exemplifies a significant reduction of the above cited parameters in the patient population termed as cancer cachexia. NSCLC induces metabolic disturbances, leads to a state of constant sympathetic activation, reduction in gonadal function, insulin resistance and tumor induced systemic inflammation. These changes coupled with poor food intake lead to muscle wasting, decreased performance status and tolerability to treatment[30].

The normal serum protein level is 6 to 8 g/dL out of which albumin makes up 3.5 to 5.0 g/dL, and the remainder, the total globulin[31]. Sixty and fifty three percent of the patient population with an average value of 5.82 g/dL and 3.38 g/ dL, respectively experienced hypoproteinemia and hypoalbuminemia (Table 2). Decreased serum total protein and albumin levels may arise from increased cytokine production ancillary to NSCLC, such as IL-6, can impair hepatic albumin synthesis[32]. Additionally, tumor necrosis factor (TNF) may enhance vascular permeability, leading to albumin loss. Micrometastatic liver involvement secondary to lung carcinoma can also stimulate Kupffer cells to produce cytokines like IL-1b, IL-6, and TNF, further compromising albumin production as the disease progresses[32,33]. A recent study analyzed the correlation between A:G Ratio (AGR) and overall survival (OS) in small cell lung cancer (SCLC) patients. Patients with high AGR (≥1.29) were found to have a longer OS when compared to those with lower AGR (<1.29). Multivariate analysis demonstrated AGR as an independent factor in the prognosis of lung cancer[34]. In our study, though the values of both patient and control brackets are within the normal limits, there is a mild to moderate reduction in patient values compared to the controls (Table 2). In the hepatocytes of the liver, ALT is predominantly a cytoplasmic

enzyme and is specific for the liver. Whereas AST exists as both mitochondrial and cytoplasmic isoenzymes and also is abundant in liver, kidney, myocardium and skeletal muscles thus marking it non-specific. Similarly the half life of AST (18 hours) is half that of ALT (36 hours), marking its higher level in the serum. A mild elevation (2-5 times of upper reference limit) is seen with respect to micrometastasis in liver subsidiary to neoplasia lung[35].

RS stimulates lipid peroxidation and disrupts the organization of the membrane lipid bilayer. This disturbance can result in the inactivation of membrane bound receptors and enzymes, as well as an increase in tissue permeability thus marking the cell membrane fragile and prone to lysis[36,37]. The study confirmed an elevation in percentage hemolysis in the patient bracket in comparison to the controls. Scanning electron microscopic (SEM) examination of the RBCs helped us to come to the same conclusion. RS also instigates lipid peroxidation leading to the formation of products like MDA and other unsaturated aldehydes. Apart from being a marker of oxidative stress, MDA possesses the ability to inactivate numerous cellular proteins through the formation of cross links between them[38]. In this study MDA showed a statistically significant elevation in the patient population. Gonenc et al.[39] demonstrated a similar elevation in MDA values, in a study of 12 lung cancer patients analogous to our results, thus providing further evidence to this relationship. Though we had foreseen an increase in methemoglobin secondary to deactivation of cytochrome B5 reductase, no such evidence was obtained from the study as it remained unaltered in both the groups. Protein carbonyl, the marker of protein oxidation, was appreciably elevated in our study. Although literature pertaining to alterations of protein carbonyl in lung cancer is meager, Rossner et al.[40] and Chih-Ching Yeh et al.[41] confirmed an upsurge in the levels of carbonyl in patients with breast and colorectal cancer respectively. They also deciphered the use of this variable as a predictor and prognostic tool in the management of these cancers. Dityrosine (DiY) is formed by ortho-ortho covalent cross coupling between two tyrosine residues linked together at the carbon of the phenol ring. DiY synthesis begins with the formation of a tyrosyl radical generated due to the removal of the hydrogen atom from the hydroxyl group on the phenoxy ring, secondary to oxidative stress[42]. The two tyrosyl radicals then undergo radical isomerization followed by diradical coupling, and finally enolization resulting in DiY[43]. We observed homologous results to Pennathur et al.[44] who studied both human and rat models of interstitial lung disease, a precursor and risk factor of neoplasia lung, and found a sizable elevation in all the oxidation products of tyrosine, including dityrosine. Mounting evidence implicates AGEs as a key player in cancer progression. This is underscored by the significantly higher serum AGE levels detected in women afflicted with breast cancer compared to healthy controls[45,46]. The above study reflects identical results with a positive upswing in AGEs in the NSCLC group bridging the existing knowledge gap.

Taking the antioxidant parameters into consideration, a recent study by Karatas et al.[47] in NSCLC exhibited consequently low values of total and native thiol in 41 out of 60 recruited patients. This data is consistent with our findings. Xiang et al.[48] showed that patients with lung cancer have a lower total antioxidant status (TAS) compared to their healthy counterparts. Though particulars with regard to FRAP of sera in NSCLC patients are inconspicuous, we can come to a conclusion that for the total antioxidant status to be notably lowered, both enzymatic and nonenzymatic antioxidants should be on the lower ranges. FRAP portrays the functionality of these non enzymatic antioxidants. Thus, we can correlate the findings of the above study to that of ours. Akin the case with ascorbic acid. Our findings suggest that in lung carcinoma patients, oxidants increase and antioxidant levels decrease, resulting in a shift in the oxidant-antioxidant balance toward oxidative stress.

Conclusion

Lung carcinoma has been shown to have fabricated significant changes in both biochemical and morphological attributes in a living system. The study highlighted a pronounced depletion of antioxidants alongside an increase in oxidative stress markers. Additionally, red blood cells exhibited morphological abnormalities, reflecting impaired membrane integrity. Moreover, a slight reduction in albumin levels was noted in the patient group. These findings collectively emphasize the critical influence of oxidative stress in the development and progression of NSCLC.

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Conflict of interest

All authors declare no conflict of interest.

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