



SIGNIFICANCE OF SERUM FERRITIN LEVEL IN NONSMALL CELL LUNG CARCINOMA AS PROGNOSTIC MARKER AND TO PREDICT TUMOR BURDEN.

General Surgery

Dr. Nileshwari A. Patel

Second year Resident, Shri M. P. Shah Government Medical Collage, Jamnagar.

Dr. Shamim Sheikh Associate Professor, Shri M. P. Shah, Government Medical Collage, Jamnagar.

Dr. Khyati Jagani* Senior Resident, Shri M. P. Shah, Government Medical Collage, Jamnagar.
*Corresponding Author

Dr. Harsh Majithiya

Senior Resident, Shri M. P. Shah, Government Medical Collage, Jamnagar.

ABSTRACT

Background And Aims: In global cancer incidence and mortality, lung carcinoma is presently the leading cause. There are a number of causes for lung cancer. Tobacco smoking is considered a leading cause for lung malignancies, but it is also observed that the cases of lung cancer are also increasing in nonsmokers. In advanced non-small cell lung cancer (NSCLC) patients, serum ferritin (SF) is increased. In this study, we study the significance of SF level in non-small cell lung carcinoma as a prognostic marker and predict tumor burden by using the enzyme-linked immunosorbent assay (ELISA) method. Additionally, we will study the relation between level of SF and pathological types, smoking status. **Material And Method:** A blood sample was collected in a plain vacuette from a patient with NSCLC. The expression of SF in a blood sample was analyzed using the ELISA method and the reagent kit of the Calbiotech company. **Results:** In the present study, it was observed that SF is increased in total 72% of cases of NSCLC. Most cases of increased ferritin are in the range of 300-500 ng/mL. **Conclusion:** Serum ferritin increases in non-small cell carcinoma of the lung; however, other causes of increases in SF like anemia, infection, and inflammation have to be ruled out.

KEYWORDS

serum ferritin level, non-small cell lung carcinoma, iron

INTRODUCTION:

In global cancer incidence and mortality, lung carcinoma is presently the leading cause. According to GLOBOCAN 2020, worldwide lung carcinoma is the most common carcinoma after breast carcinoma and the most common cause of mortality¹. According to GLOBOCAN India statistics for 2020, there were an approximate 1.3 million new cancer cases and 8,51,678 cancer deaths. Among total new cancer cases, 5.5% were found to be of lung cancer, which constitutes approximately 72,510 cases. Therefore, in the prediction of progression of advanced NSCLC, it is very necessary to take a look at novel tumor markers. It will also help to find treatment strategies.² There are a number of causes of lung cancer, but as a leading cause Tobacco smoking is considered for lung malignancies. There is also a role of genetics and environmental factors in the occurrence of lung cancer, as the cases of lung cancer are also increasing in nonsmokers, occurring more commonly in women. Rosenow stated that even if all smokers stopped smoking immediately, no decline in lung cancer incidence is to be expected during 5–15 years.³ Early detection is needed in the present scenario with clinical symptoms, a chest X-ray, CT scan, sputum cytology, and tumor markers that can support the evidence of a tumor by histological cell typing. Therefore, endoscopies and biopsies became inevitable since the advent of the flexible fiber optic bronchoscope by Ikeda in the early 1970's.⁴ Patients with cancer have an increasing level of iron, which is related to an increased risk of neoplasia at the site of metal deposition. By catalyzing the generation of highly reactive hydroxyl radicals via the HaberWeiss reaction, iron could participate in carcinogenesis⁵.

There is recent evidence that reductants present in cigarette smoke can easily mobilize iron from ferritin, leading to lipid peroxidation and cell damage. Lungs provide protection from iron-induced injury by the association of iron with iron-binding proteins ferritin and transferrin. Serum ferritin (SF) retains iron in a soluble and non-toxic form. May be the high level of serum ferritin in non-small cell lung cancer is due to inflammation and oxidative stress. In advanced diseases, deterioration, and solid tumors, such as lung tumors, there is a contradiction between iron deficiency and high SF levels.⁶

In this study, we took a blood sample from patients with advanced NSCLC and examined SF levels by using the enzyme-linked immunosorbent assay (ELISA) method. Additionally, we study the relation between SF and pathological types, smoking status, and later on we will assess whether it can be used in advanced NSCLC patients to predict the prognosis or not.

MATERIAL AND METHOD:

Design Of Study: prospective study

Duration Of Study: 1.5 year

Sample Size: Total 100 cases

Study Area: Department of Pathology

Patients who are newly diagnosed NSCLC cases based on radiographic and histopathological or cytological criteria were included in this study. Hb should be more than 7 gm/dl. Patients who were treated with antitumor therapy, not diagnosed with radiographic and histopathological or cytological criteria, had malignancies other than non-small cell lung carcinoma, were treated with iron, or suffered from inflammatory conditions affecting ferritin metabolism were excluded from the study.

This study will be performed to detect the expression of SF in patients with NSCLC by using the enzyme-linked immunosorbent assay (ELISA) method and the reagent kit of the Calbiotech company.

RESULTS:

In this study, we observed that most patients of lung carcinoma were from 4th - 8th decade and male predominance. Overall Male: Female ratio was 8.1:1 in lung cancer patients. Out of 100 patients, 82 (82%) cases had positive history of smoking and majority having longer duration of addiction (≥ 10 years). it was observed that adenocarcinoma was the most common carcinoma (61%), followed by squamous cell carcinoma (39%).

Table I: Serum Ferritin Level In Non-small Cell Lung Carcinoma (n=100)

Sr. no.	Serum Ferritin level	No. of cases	Percentage (%)
1	Normal	28	28 %
2	High	72	72 %
	Total	100	100

In present study, it was observed that Serum Ferritin is increased in total 72 % of cases of non-small cell lung carcinoma.

In present study, in all 100 cases of lung cancer, CT scan chest was done (100 %) and CT-guided FNA and/or biopsy were taken.

In CT scan findings, total 14 cases were having pleural effusion. out of

14 cases, 10 having adenocarcinoma and remaining 04 having squamous cell carcinoma. Out of these 14 cases, 12 cases are having high ferritin level.

In CT scan findings, total 20 cases were having Mediastinal Lymphadenopathy, out of which 12 were having adenocarcinoma and 08 were having squamous cell carcinoma. Out of these 20 cases, 18 cases are having high ferritin level.

Table II: Clinical And Imaging Characteristic In Squamous Cell Carcinoma (n=39)

SCC	Age group (years)					Gender		Smoking status		Radiological location						Serum Ferritin Level	
										Side		Site					
	≤ 40	41-50	51-60	61-70	>70	M	F	Smoker	Non smoker	Right	Left	Upper Zone	Middle zone	Lower zone	Hilar region	High	Normal
Number of cases	1	9	7	13	9	38	1	35	4	23	16	24	0	5	10	28	11
Percentage (%)	2.56	23.08	17.95	33.33	23.08	97.44	2.56	89.74	10.26	58.97	41.03	61.24	0.00	12.82	25.64	71.79	28.20

In this study, majority of cases of squamous cell carcinoma (33.33%) were noted in older adult group (61-70years) with male predominance (97.44 %) and more common in smoker (89.74 %). On imaging studies, the right lung more (58.97 %) involved by tumor and more commonly in upper lobe of lung (61.24 %)

Table III: Clinical And Imaging Characteristic In Adenocarcinoma (n=61)

Adeno-carcino ma	Age group (years)						Gender		Smoking status		Radiological location						Serum Ferritin Level	
											Side		Site					
	31-40	41-50	51-60	61-70	71-80	>80	M	F	Smoker	Non smoker	Right	Left	Upper Zone	Middle zone	Lower zone	Hilar region	High	Normal
Number of cases	3	11	20	16	8	3	51	10	47	14	42	19	34	07	14	06	44	17
Percentage (%)	4.92	18.03	32.79	26.23	13.11	4.92	83.61	16.39	77.05	22.95	68.85	31.15	55.74	11.47	22.95	9.84	72.13	27.87

In this study, we were noted that majority of cases of adenocarcinoma (32.79%) are in 51-60 years age group with male predominance (83.61%) and more common in smoker (77.05%). On imaging studies, the right lung more (68.85%) involved by tumor and more commonly in upper zone of lung (55.74%).

polygonal malignant cells containing keratin. Cells show pleomorphism with high N: C ratio, nuclear hyperchromasia, irregular nuclear membrane and moderate amount of dense eosinophilic cytoplasm. (H & E stain x 40)

The present study was mainly on the clinopathological and histomorphological correlation in 100 cases of lung carcinoma. Out of 100 cases, 56% of the patients were belonging to 6th and 7th decade and median age being 60 years. Male to female ratio was 8.1:1. Majority of patients were presented with the chief complaint of cough (92%), fever(55%) and dyspnea(54%), followed by chest pain(44%), weight loss(42%) and hemoptysis(18%). 82 % cases had positive history of smoking. All 100 suspected cases of lung cancer, CT scan chest was done and CT guided biopsy was taken in all cases. Most common site of lung carcinoma was right side of lung (65%). According to radiological findings zone wise distribution of lung cancer were found in upper zone, middle zone, lower zone and hilar region from which maximum cases were observed in upper lobe (58%) of lung, followed by lower lobe (19%), hilar region (16%) and middle lobe. Based on histomorphological features, lung carcinoma were divided into squamous cell carcinoma (39%) and adenocarcinoma (61%). Serum Ferritin level was increased in non-small cell lung carcinoma in 72% of cases.

The histological features of various lung carcinoma on H & E stain section are as follows:

Squamous Cell Carcinoma:

Sheets and clusters of large polygonal malignant cells containing keratin and intracellular bridges. Cells show pleomorphism with high N: C ratio, nuclear hyperchromasia, irregular nuclear membrane and moderate amount of dense eosinophilic cytoplasm. Occasionally necrosis, giant cell formation and granuloma formation are also seen.

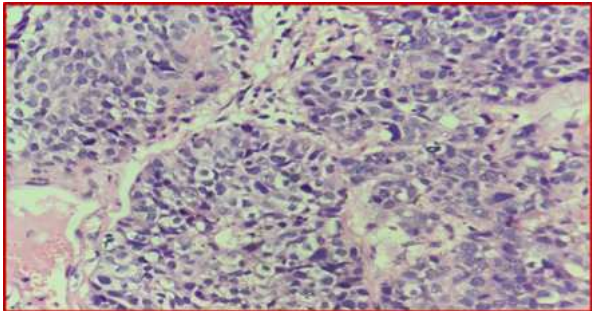


Figure 1: Squamous cell carcinoma of Lung, section showing large

Adenocarcinoma:

Scattered as well as clusters of cells showing gland formation at places. The cells are round to oval with high N: C ratio, regular nuclear membrane, nuclear overlapping, nuclear crowding, vesicular nuclear chromatin, prominent nucleoli and moderate amount of cytoplasm.

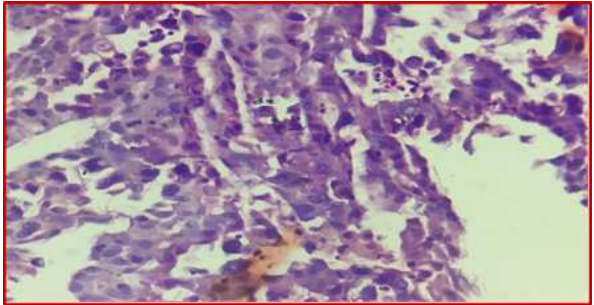


Figure 4: Adenocarcinoma of Lung, section showing malignant epithelial cells with high N:C ratio, nuclear pleomorphism, prominent nucleoli and moderate amount of eosinophilic cytoplasm. (H & E stain x 40)

DISCUSSION:

The present study is an effort to evaluate role of serum ferritin in non-small cell lung carcinoma as prognostic marker along with finding its significant correlation with other prognostic parameters for non-small lung carcinoma such as older age, male gender, history of smoking, presence of visceral effusion and mediastinal lymphadenopathy.

This study consisted of total 100 specimens of small biopsies of lung, confirmed as non-small cell lung carcinoma with cytopathology and/or histopathology. Serum samples for tumor marker were received from Respiratory Medicine Department, Tertiary Care Center.

In present study, 56% of the patients were belonging to 6th and 7th decades and median age being 60 years and males were most commonly (89%) affected than females (11%). Right side of lung most commonly involved. Maximum cases were observed in upper lobe of lung, followed by lower lobe, hilar region and middle lobe. Smoking was found to be a major risk factor for all cases along with longer duration of addiction. Majority of patients were presented with the chief complaint of cough, fever and dyspnea, followed by chest pain,

weight loss and hemoptysis. Serum Ferritin level was increased in non-small cell lung carcinoma in 72% of cases.

All cases were subtyped morphologically by H & E stain. Out of the 100 cases, there were 39 cases (39%) of squamous cell carcinoma and 61 cases (61%) of adenocarcinoma.

Table IV: Comparison Of Age Group And Gender Incidence In Various Study

Study	Year	No. of cases	Age group (year)	M: F
Agarwal et al ⁸	2000	73	50-69	3.5: 1
Kawaraya et al ^[9]	2003	1372	45-70	7: 1
Bhattacharyya SK et al ^[10]	2011	266	41-60	6.6: 1
Reddy AS et al ^[11]	2014	448	51-60	12.64 :1
Bhattacharyya SK et al ^[12]	2018	242	41-60	6.12:1
Present study	2022	100	51-70	8.1: 1

In the present study, age of patients ranged from 51-70 years, which is comparable to Agarwal et al ⁷. And all the lung cancers were predominantly found in males. The M: F ratio was 8.1: 1 which is comparable with study done by Kawaraya et al ⁸.

Table V: Comparison Of Symptoms In Various Studies

Study	Year	No. of cases	Cough (%)	Dyspnoea (%)	Chest pain (%)	Hemoptysis (%)
Bhattacharyya SK et al ⁹	2011	266	68.42	63.15	52.63	36.84
Bhattacharyya SK et al ¹¹	2018	242	71.90	51.68	58.68	19.83
Thakkar D et al ¹²	2019	50	90	68	62	42
Present study	2022	100	92	54	44	18

In present study, cough (92%) is comparable with study done by Thakkar D et al ¹².

In present study, dyspnoea (54%) and hemoptysis (18%) are comparable with study done by Bhattacharyya SK et al ¹¹.

Table VI: Comparison Of Incidence Of Smoking In Lung Cancer Patients In Various Studies

Study	Year	No. of cases	Positive history of smoking (%)
Agarwal et al ⁷	2000	73	90.70
Bhattacharya SK et al ⁹	2011	266	81.2
Bhattacharya SK et al ¹¹	2018	242	86.36
Present study	2022	100	82

In the present study, the incidence of smoking was 82% which is almost comparable with all the studies mentioned in the above table.

Table VII: Comparison Of Incidence Of Various Types Of Lung Cancers In Various Studies

Study	Year	No. of cases	Squamous cell carcinoma	Adenocarcinoma
Agarwal et al ⁷	2000	73	55.0	21.5
Pirina P et al ¹³	2007	349	42.7	20.2
Zhang P et al ¹⁴	2010	322	26.2	65.4
Bhattacharya SK et al ⁹	2011	266	35.34	15.79
Bhattacharya SK et al ¹¹	2018	242	38.02	29.75
Present study	2022	100	39	61

In present study, incidence of various type of lung carcinoma is comparable with study done by Zhang P et al ¹⁴. Studies done by Agarwal et al ⁷, Pirina P et al ¹³, Bhattacharya SK et al ⁹ and Bhattacharya SK et al ¹¹, which are not comparable with present study.

Table VIII: Comparison Of Serum Ferritin Level In Non-small Cell Lung Carcinoma

Study	Year	No. of cases	Percentage of cases with high serum ferritin level
Zhongqing C et al ⁶	2017	821	62 %
Present Study	2022	100	72 %

In the present study, 72 % cases were showing high serum ferritin level, which is comparable to study done by Zhongqing C et al ⁶.

CONCLUSION:

- This study was aimed to correlate Serum Ferritin levels in blood sample of non-small cell lung carcinoma patient by using the Enzyme linked immunosorbent assay (ELISA) method and to see the prognostic value of serum ferritin.
- This study showed that serum ferritin increases in non-small cell carcinoma of lung, however other causes of increased serum ferritin like anemia, infective and inflammatory have to be ruled out.
- Other poor prognostic parameters including pleural effusion and mediastinal lymphadenopathy also showed high ferritin level, supporting serum ferritin as prognostic parameter.
- For prognosis of lung carcinoma, Serum Ferritin can also be used as prognostic parameter with other tumor markers.

REFERENCES:

- Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2020). GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.(2020). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: <https://gco.iarc.shi.hb>, Li XD, Jiang JT, Zhao WQ, Ji M, Wu CP. Serum ferritin is elevated in advanced non-small cell lung cancer patients and is associated with efficacy of platinum-based chemotherapy. J Can Res Ther 2014;10:681-5
- Rosenow ES III: Neoplasia symposium on itrahoracic introduction Myoclin Proc. 1993; 68 :168.
- Ikedo B, Yanai N, Ishika S. Flexible fibre optic bronchoscope. Keiro J Med. 1986; 17 : 1-16.
- Suzana Kukulj, Morana Jaganjac, Milivoj Boranic, Simun Krizanac, Zarko Krizanac, Zarko Santic, Marija Pojak-Blazi. Altered iron metabolism, inflammation, transferrin receptors and ferritin expression in non-small-cell lung carcinoma. Med Oncology, 2010 Jun;27(2):268-77.
- Zhongqing Chen, Bo Zhu, Chao Ou and Yuxuan Li. Serum ferritin and primary lung cancer. Oncotarget, 2017 Nov 3; 8(54):92643-92651.
- Agarwal A, Ghotekar LH, Garbhal RS, et al. Evaluation of pulmonary malignancies in Kathmandu valley and role of bronchoscopic techniques in diagnosis of such cases. JIACM 2003; 4(2): 127-33.
- Kawaraya M, Gemba K, Veoka H et al. Evaluation of various cytologic examination of bronchoscopy in the diagnosis of peripheral lung cancer. Br J Cancer. (2003);89(10),1885-1888.
- Bhattacharyya SK, Mandal A, Deoghuria D et al. Clinico- pathological profile of lung cancer in a tertiary medical centre in India: Analysis of 266 cases; J Den Oral Hyg..2011 ;3(3): 30-33.
- Reddy S, Vivekanand N, Durga K. Efficacy of Bronchial Wash and Brush Cytology in the Diagnosis of Lung Cancers; Sch J App Med Sci. 2014; 2(2D) : 816-820.
- Bhattacharya SK, Chatterjee S. Study of Lung Cancer in rural medical college in hilly area of West Bengal. J Med Sci Clin Res. 2018; 6(6): 943-947.
- Thakkar D, Damor P, Vithalani k et al. Clinicopathological profile of patients with bronchogenic carcinoma at a tertiary care center in western india; Indian J Respir Care, 2019; 8(2): 80-83.
- Pirina P, Budroni M, Esposito S et al. Cytological and histological diagnosis of lung cancer in Sardinia and Italy in the 1990s. Monaldi Arch Chest Dis. 2007; 67: (4), 179-183.
- Zhang P, Han Y et al. Value of napsin A and thyroid transcription factor-1 in the identification of primary lung adenocarcinoma. Oncol Lett. 2010 ; 1: 899-9