



## Assessment of IL-6, Serum Ferritin Levels and their Co-relation with Severity of Carcinoma Breast

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### Abstract

**Background:** Carcinoma Breast is the second most common carcinoma in females. The incidence of carcinoma breast is 19-34%. There are various inflammatory markers which have shown prognostic value in cancers. Interleukin-6 is a pro-inflammatory cytokine that plays role in tumour progression by promoting tumour cell growth via up-regulating anti-apoptotic and angiogenic proteins. Ferritin is a positive acute phase reactant which is synthesised in liver. Higher serum ferritin levels in carcinoma breast are associated with poor outcome. **Material & Methods:** The present study was conducted in the department of General Surgery, GGS Medical College and Hospital, Faridkot for a period of 18 months on 60 female patients diagnosed with carcinoma breast. **Results:** In our study maximum patient i.e 14 (23%) belonged to stage IV of carcinoma breast. Raised serum IL-6 was associated significantly with metastasis. It was observed that the levels of IL-6 progressive increased in each stage of carcinoma breast. It was observed that there was significant rise in serum ferritin with metastasis, however, serum ferritin did not follow any specific trend from stage to stage. **Conclusions:** Serum IL-6 levels provides a simple, convenient objective test that can be used to determine the extent of carcinoma disease and thus may be used as a prognostic indicator in patients of carcinoma breast. Serum ferritin levels can be used as a marker to determine advanced metastatic carcinoma breast.

**Keywords:-** IL-6, Carcinoma Breast, Surgery.

## INTRODUCTION

Carcinoma Breast is the second most common carcinoma in females.<sup>[1]</sup> Carcinoma breast is associated with high morbidity and mortality worldwide. The incidence of carcinoma breast is 19-34%. Breast cancer is second leading cause of cancer associated deaths with approximately 40,000 deaths per year. In recent years, due to development of new treatment and diagnostic modalities the incidence of carcinoma breast related death has shown a significant decreasing trend.<sup>[2]</sup>

Anatomically, the breast is a modified sweat gland which lies in front of the chest wall. The parenchyma of the breast is composed of stromal tissue and lobes, which are further divided into multiple lobules. The terminal ductal unit is the site for the origin of the carcinoma breast.<sup>[3]</sup>

Median age of diagnosis of carcinoma breast in a female is 47 years. Main risk factors of carcinoma breast are inherited mutations in genes like BRCA1 and BRCA2. Various other risk factor are early menarche and late menopause, family history of breast and ovarian cancer, previous history of radiation exposure women having dense breast tissue, obesity, alcohol consumption and hormone therapy.<sup>[4]</sup>

The natural progression of the carcinoma breast ranges from an asymptomatic breast lump to metastatic disease. It is well known for its metastatic potential and can spread to various sites like the vertebral column, lungs, brain, and liver but rarely to the gastrointestinal tract.<sup>[5]</sup>

Inflammation plays a key role in the initiation, promotion, and metastasis of cancer through various mechanisms. These pathways are regulated by inflammatory mediators like cytokines and acute phase reactants.<sup>[6]</sup>

There are various inflammatory markers which have shown prognostic value in cancers. Interleukin-6 is a pro-inflammatory cytokine that was first identified as a B-cell stimulatory factor. It is 30kDa glycoprotein which is produced by macrophages, T cells, B cells endothelial cells and tumour cells. Interleukin-6 has many functions which helps in regulation and coordination of metabolism, immune system and nervous system and autoimmune disorders. Interleukin -6 plays role in tumour progression by promoting tumour cell growth by up-regulating anti-apoptotic and angiogenic proteins. When compared to non-metastatic breast cancer, patients with metastatic breast cancer have shown raised levels of 9 Interleukin-6. Studies have shown that cells of various cancers like renal, bladder, prostate, ovarian and breast constitutively express Interleukin-6 and also express IL-6 receptors.<sup>[7]</sup> Ferritin is a positive acute phase reactant which is synthesised in liver. Ferritin is primary intracellular iron storage protein and is also abundant in circulation. In healthy individuals the concentration of serum ferritin is directly related to the amount of reticuloendothelial storage iron in the body. It has been observed that there are higher levels of ferritin both in serum and tumour cells in carcinoma breast patients. Higher serum ferritin levels in carcinoma breast are associated with poor outcome.<sup>[8]</sup>



## MATERIAL AND METHODS

The present study was conducted in the department of General Surgery, GGS Medical College and Hospital, Faridkot for a period of 18 months on 60 female patients diagnosed with carcinoma breast. The study excluded the non-consenting female, male patients and patient with chronic diseases.

Data was collected using self-structured proforma, which consisted of detailed history, thorough examination, investigations, and results.

## Methodology

Blood venous samples were collected from all patients before any surgical intervention, detailed general & local examination was done. Tumor size, site, nodal involvement were assessed. Core biopsy, ultrasound/ CT of abdomen and chest x-ray/ CT were done for each patient. The clinical staging was done based following TNM staging. Interleukin-6 and serum ferritin were measured by chemiluminescence method. The normal range of IL-6 is upto 7pg/ml and for serum ferritin 11-307ng/ml (9,11).

## RESULTS

**Table 1:** distribution of patients according to staging of breast carcinoma

Stage	No. of cases	Percentage
I	11	18.3%
II a	11	18.3%
II b	8	13.3%
III a	6	10%
IIIb	5	8.3%
IIIc	5	8.3%
IV	14	23.3%
Total	60	100.0%

In our study, maximum patient i.e 14 (23%) belonged to stage IV of carcinoma breast.

**Table 2:** interleukin-6 levels according to TNM stage

T	Cases	Mean IL-6 Levels (pg/ml)
T	T1	16
	T2	26
	T3	12
	T4	6
N	N0	29
	N1	10
	N2	10
	N3	6
M	M0	46
	M1	14

In this present study, serum IL-6 raised significantly with metastasis.

**Table 3:** Interleukin-6 levels according to staging of carcinoma breast

Stage	Mean + SD
I	7.09+1.04
IIA	9.07+1.13
IIB	12.25+2.95
IIIA	29.33+1.97
IIIB	28.00+4.12
IIIC	29.40+2.41
IV	45.06+2.31
Overall	22.83+15.12
P-value	0.001

In this study, it was observed that levels of IL-6 progressive increased in each stage of carcinoma breast.

**Table 4:** Serum Ferritin Levels According to TNM Stage

T	Cases	Mean Ferritin Levels (ng/ml)
T	T1	16
	T2	26
	T3	12
	T4	6
N	N0	29
	N1	10
	N2	10
	N3	6
M	M0	46
	M1	14

In this study, it was observed that there was significant rise in serum ferritin with metastasis.

**Table 5:** serum ferritin levels according to staging of carcinoma breast

Stage	Mean + SD
I	71.73+51.30
IIA	69.00+41.35
IIB	81.69+45.45
IIIA	100.33+34.49
IIIB	77.00+38.76
IIIC	99.60+65.35
IV	432.14+24.81
Overall	162.28+155.76
P-value	0.000

In this study it was observed that serum ferritin did not follow any specific trend from stage to stage.

## DISCUSSION

Breast malignancy is the most common cancer diagnosed in females, accounting for more than 1 in 10 new cancer diagnoses each year. It is the leading cause of cancer-related death in women worldwide.<sup>[9,10]</sup>

In the present study, the maximum patients 23.3% belonged to stage IV disease, followed by stage I & IIa 18.3% patients each. 13.3% patients were categorized under IIb, 10% patients under IIIa, while 8.3% of patients belonged to IIIb & IIIc each. The maximum percentage of patients belonging to stage IV that is metastatic disease can be attributed to the delayed presentation of the patients due to ignorance, embarrassment, illiteracy, and low socio-economic status.

In the present study, it was noted that levels of Interleukin-6 rose progressively with increasing stage of the disease, being lowest in stage I (7.0+1.04) and highest in the stage IV (45.06+2.31). These observations were collaborated by a study conducted by Ravishankar P et al in which it was observed that median levels of IL-6 showed a proportional increase with the stage of cancer, this difference being statistically significant ( $p < 0.001$ ). In this study, it was also observed that levels of IL-6 in patients with distant metastasis were higher (39+9.3pg/ml) as compared to patients without distant metastasis (17.3+7.6 pg/ml).<sup>[11]</sup>

In a study conducted by Jablonska E et al, it was observed that mean levels of serum IL-6 were higher in stage III/IV disease as

compared to stage II, which was consistent with the findings in our study. In another study conducted by Kozłowski L et al, it was observed that levels of IL-6 were associated strongly with breast cancer and correlated well with clinical stage of the disease.<sup>[12]</sup>

In study by Yao x median value of serum ferritin in non-metastatic carcinoma breast patients was 76.57 (p25=44.94, p75=132.28), and that in metastatic breast carcinoma, patients was 307.80 (p25=151.232, p75=600.05). It was observed that serum ferritin has high specificity & sensitivity to predict distant metastasis, and levels specifically reflected the metastasis-associated burden of the carcinoma breast. This study concluded that by including routine analysis of serum ferritin levels in carcinoma breast patients undergoing treatment, improvement in the therapeutic decision could be made.<sup>[13]</sup>

In a study by Mishra S it was observed that the mean level of serum ferritin in patients with carcinoma breast without metastasis was 214+36.2 (range 180-250) while that in patients with metastasis was 647+58.2, showing a significant increase of serum ferritin levels in carcinoma breast patients with metastasis.<sup>[14]</sup>

In the present study, it was observed that levels of serum ferritin did not follow any specific trends with the stage of the disease. It was seen that mean levels of serum ferritin were significantly high in metastatic stage IV disease (432.14+24.81ng/ml) as compared to non-metastatic disease, in which the mean value of serum ferritin was 85.71+54.02ng/ml.

## CONCLUSIONS

In light of the result obtained, we have come to the following conclusions :

- Serum IL-6 levels provides a simple, convenient objective test that can be used to determine the extent of carcinoma disease and thus may be used as a prognostic indicator in patients of carcinoma breast.
- Serum ferritin levels can be used as a marker to determine advanced metastatic carcinoma breast.

## REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin.* 2021;71(3):209-249. doi: 10.3322/caac.21660.
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin.* 2015;65(2):87-108. doi: 10.3322/caac.21262.
3. Majeed W, Aslam B, Javed I, Khaliq T, Muhammad F, Ali A, et al. Breast cancer: major risk factors and recent developments in treatment. *Asian Pac J Cancer Prev.* 2014;15(8):3353-8. doi: 10.7314/apjcp.2014.15.8.3353.
4. Radovic N, Ivanac G, Divjak E, Biondic I, Bulum A, Brkljacic B. Evaluation of Breast Cancer Morphology Using Diffusion-Weighted and Dynamic Contrast-Enhanced MRI: Intermethod and Interobserver Agreement. *J Magn Reson Imaging.* 2019;49(5):1381-1390. doi: 10.1002/jmri.26332.
5. Cormier WJ, Gaffey TA, Welch JM, Welch JS, Edmonson JH. Linitis plastica caused by metastatic lobular carcinoma of the breast. *Mayo Clin Proc.* 1980;55(12):747-53.
6. Salgado R, Junius S, Benoy I, Van Dam P, Vermeulen P, Van Marck E, et al. Circulating interleukin-6 predicts survival in patients with metastatic breast cancer. *Int J Cancer.* 2003;103(5):642-6. doi: 10.1002/ijc.10833.
7. Jacobs A, Jones B, Ricketts C, Bulbrook RD, Wang DY. Serum ferritin concentration in early breast cancer. *Br J Cancer.* 1976;34(3):286-90.
8. Lan T, Chen L, Wei X. Inflammatory Cytokines in Cancer: Comprehensive Understanding and Clinical Progress in Gene Therapy. *Cells.* 2021;10(1):100. Published 2021 Jan 8. doi:10.3390/cells10010100.
9. Qu X, Tang Y, Hua S. Immunological Approaches Towards Cancer and Inflammation: A Cross Talk. *Front Immunol.* 2018;9:563. doi: 10.3389/fimmu.2018.00563.
10. Endale M, Park SC, Kim S, Kim SH, Yang Y, Cho JY, et al. Quercetin disrupts tyrosine-phosphorylated phosphatidylinositol 3-kinase and myeloid differentiation factor-88 association, and inhibits MAPK/AP-1 and IKK/NF- $\kappa$ B-induced inflammatory mediators production in RAW 264.7 cells. *Immunobiology.* 2013;218(12):1452-67. doi: 10.1016/j.imbio.2013.04.019.
11. Ravishankaran P, Karunanithi R. Clinical significance of preoperative serum interleukin-6 and C-reactive protein level in breast cancer patients. *World J Surg Oncol.* 2011;9:18. doi: 10.1186/1477-7819-9-18.
12. Kozłowski L, Zakrzewska I, Tokajuk P, Wojtukiewicz MZ. Concentration of interleukin-6 (IL-6), interleukin-8 (IL-8) and interleukin-10 (IL-10) in blood serum of breast cancer patients. *Rocz Akad Med Białymst.* 2003;48:82-4.
13. George A, Bobby Z, Dubashi B. Utility of ferritin and inflammatory biomarkers in the diagnosis of different stages of breast cancer. *Saudi Med J.*



2021;42(8):825-831.

doi:

10.15537/smj.2021.42.8.20210244.

14. Mishra S, Sharma DC, Sharma P. Studies of biochemical parameters in breast cancer with and without metastasis. Indian J Clin Biochem. 2004;19(1):71-5. doi: 10.1007/BF02872394.

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