E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.48047/ijprt/16.02.274

**Research Article**

# Serum Hepatocyte Growth Factor (HGF) estimation and its correlation study with Hormonal Receptor Status (ER, PR, and HER2/neu) in Carcinoma Breast

**Dr Chaithra V.[1], Dr Rekha T S[2], Dr Rashmi N.[3]**

[1]Assistant Professor, Department of Pathology, Chamarajanagar Institute of Medical Sciences, Chamarajanagar, India.
[2]Professor, Department of Pathology, JSS Medical College, Mysuru, India.
[3]Senior Resident, Department of Pathology, Chamarajanagar Institute of Medical Sciences, Chamarajanagar, India.

**Received Date: 02/05/2026 Accepted: 09/06/2026 Published Date: 12/07/2026**

**Corresponding author:** Dr. Chaithra V., Assistant Professor, Department of Pathology, Chamarajanagar Institute of Medical Sciences, Chamarajanagar, India.
**Email:** chaithraaravind24@gmail.com

## ABSTRACT

**Background:** Hepatocyte Growth Factor (HGF) and its receptor c-MET are involved in breast cancer progression, angiogenesis, invasion, and metastasis. Serum HGF has emerged as a potential biomarker for tumor aggressiveness. **Aim:** To evaluate serum HGF levels in breast carcinoma patients and correlate them with ER, PR, and HER2/neu receptor status. **Materials and Methods:** This prospective observational study included 35 histopathologically confirmed breast carcinoma patients. Serum HGF levels were measured before treatment using ELISA. ER, PR, and HER2/neu expression in 25 cases were evaluated by immunohistochemistry according to ASCO/CAP guidelines. Statistical analysis was performed using Student's t-test, Chi-square test, and one-way ANOVA. A p-value <0.05 was considered statistically significant. **Results:** Immunohistochemistry was done and it showed ER positive in 20 cases(80%), PR positive in 18 cases(72%) and HER2neu positive in 11(44%) cases. There was no significant association existed between serum HGF levels and hormonal status according to present study.

**Keywords:** Breast carcinoma, Hepatocyte Growth Factor, HGF, ER, PR, HER2/neu, Triple-negative breast cancer, Biomarker.

## INTRODUCTION

Breast cancer is the most frequently diagnosed malignancy among women worldwide and remains a leading cause of cancer-related mortality**.** In 2012, almost 145,000 Indian women were diagnosed with breast cancer and 70,000 women died due to breast cancer.[1] The lifetime risk for developing breast cancer has been reported to be as high as 12%, whereas the risk of death has been reported to be as high as 5%.[2] The long-term survival of women with breast cancer is dependent on the stage of disease at the time of diagnosis.[3] Gold standard histopathological examination for confirmation, typing, grading and assessing other prognostic markers is employed.4 The involvement of the axillary lymph nodes (LNs) is the most important prognostic factor. Apart from this, prognosis also depends on tumour size, histopathological grade, estrogen receptors(ER), progesterone receptors (PR)

and HER-2Neu status.[5] Current modality of treatment in breast carcinoma include hormonal treatment which is based on ER, PR and HER2Neu status. But there is increase in the incidence of Triple-negative breast cancer (TNBC) which represents 10%–20% of invasive breast cancers and carries a relatively poorer prognosis.[6]

Hepatocyte Growth Factor plays an important role in various stages of cancer progression. Estimation of serum HGF in many other solid carcinomas has indicated to be a good prognostic marker. This study is to estimate the serum levels of HGF in invasive carcinoma of breast to know its significance. It has been reported Hepatocyte Growth Factor(HGF) is the cause of many biological events of cancer like cell proliferation, movement, invasiveness, angiogenesis and morphogenesis. Estimation of serum HGF in many other solid carcinomas has indicated to be a good prognostic marker. Hepatocyte growth factor (HGF) was first identified in 1984 and 1985 and purified as a potent mitogen of primary cultured hepatocytes . Molecular cloning revealed that it is a heterodimeric molecule composed of a 69-kDa alpha-chain and a 34-kDa beta- chain. HGF is synthesized and secreted as a biologically inactive precursor form and activated by serine proteases. The receptor for HGF was identified as a c-Met proto- oncogene.[7]

HGF bind to c-Met receptors that are widely distributed on the various cells in the human body. Studies have shown that they facilitate the growth and progression of various cell lines. HGF is expressed predominantly by the mesenchymal cells and scantly by the epithelial cells. It has been reported HGF is the cause of many biological events of cancer, including cell proliferation, movement, angiogenesis, invasiveness and morphogenesis.[8] Considering all these factors, HGF can act as a good prognostic factor. In present study preoperative estimation of serum HGF may reflect the severity of invasive breast cancer and may be useful to pick up higher risk patients for more aggressive treatment

## HORMONE RECEPTORS

The prognostic and predictive biomarkers like ER and PR play a major role in determining the therapy of patients with invasive breast cancer.They are weak prognostic factors but very strong predictive factors of response to endocrine therapies like Tamoxifen. It is currently mandatory to evaluate ER and PR in all IBCs for the purpose of predicting therapeutic response. IHC on formalin-fixed paraffin- embedded tissue samples is the primary method used to evaluate ER and PR.[9]

### Estrogen Receptor:

ER is a nuclear transcription factor activated by the hormone estrogen and it controls the development, growth and differentiation of normal, hyperplastic and neoplastic breast epithelial cells. Chemotherapy drugs like Tamoxifen binds ER and inhibits the estrogen-stimulated growth of tumour cells, resulting in significantly longer disease free and overall survival in patients and reduces cancer recurrences in patients with ER positive IBCs, compared with those that are ER-negative. Approximately 75% of all IBCs are positive for hormone receptors.[9] Adjuvant hormonal therapy can diminish the recurrence rate of patients with ER-positive breast carcinomas by about 50%. ER negativity is almost always associated with lack of response to such treatment, but ER positivity does not always guarantee response to endocrine therapy.[10]

### Progesterone Receptor:

PR is also routinely assessed by IHC in IBCs. ER regulates the expression of PR, so the presence of PR usually indicates that the ER pathway is functionally intact. PR is activated by the hormone progesterone to help regulate several normal cellular functions, including proliferation. PR is expressed in the nuclei of 60% to 70% of IBCs, and there is a direct correlation between PR levels and response to

hormonal therapies. PR expression is also associated with reduced local recurrence in patients with DCIS treated with lumpectomy and radiation followed by endocrine therapy

**HER2Neu**:

HER2/neu overexpression is an excellent predictor of response to trastuzumab but a weak predictor of response to chemotherapy. Although it identifies a subset of patients with poor prognosis, particularly when lymph node metastases are present it correlates closely with tumor grade and loses much of its independent prognostic significance in multivariate analysis.[11,12]

Limited studies have evaluated circulating serum HGF in relation to hormonal receptor status, particularly in the Indian population. Therefore, the present prospective study was undertaken to assess serum HGF levels and correlate them with ER, PR, and HER2/neu expression in breast carcinoma.

## MATERIALS AND METHODS

### SOURCE OF DATA

The present prospective study was undertaken in the Department of Pathology, JSS Medical College and Hospital, Mysuru.

**TYPE OF STUDY** Descriptive study

**Inclusion criteria**

Histopathologically confirmed invasive duct carcinoma of breast were included in the study.

**Exclusion criteria:**

Breast carcinoma other than invasive duct carcinoma, diagnosed on core biopsy and patients having other known malignancy were excluded from the study.

### METHOD OF COLLECTION OF DATA

Clinical details were collected from the patients through structured questionnaire. Venous blood samples were collected preoperatively; serum was separated and stored at temperature $-80^0$c from patients with breast carcinoma undergoing surgery. Serum samples from normal women and benign breast tumor patients with age matched volunteers were used as control samples. Serum HGF was estimated using HGF ELISA kit(Thermofischer, Sandwich enzyme method)Gross and microscopic features of the mastectomy specimen were studied. The serum HGF levels were correlated with the hormonal receptor status (ER,PR and HER2/neu)

### PROCEDURE

The estimation of serum HGF was done by using HGF ELISA kit (Thermofischer, Co, Ltd.) using sandwich ELISA method with assay sensitivity of <10pg/ml. Standard curve is obtained by using a software from which the concentrations of the samples and standards are obtained. Mastectomy specimens were fixed in 10% neutral buffered formalin within one hour of resection. They were examined grossly according to standard guidelines and noting all the important parameters, specimens were fixed for 24-48 hours. Sections were taken from representative sites, processed in automated tissue processor followed by paraffin embedding and staining with Haematoxylin & Eosin. Estrogen, progesterone and HER-2/neu expression were assessed where ever possible. For estrogen, progesterone and Her-2/neu, kit for IHC staining were obtained from Pathnsitu Biotechnologies. Staining was done according to manufacturer protocol with rabbit monoclonal IgG type primary antibody & Pathnsitu poly HRP-Polymer detection kit for secondary antibodies. ASCO/ CAP Guidelines for grading of HER2/NEU Expression by Immunohistochemistry(IHC)[13] is followed.

### Study Design

### OBJECTIVES:

- To estimate serum HGF level in breast carcinoma and
- To correlate the serum HGF with hormonal receptor status-ER,PR and HER2/Neu status.

### Statistical Analysis

Data were analyzed using SPSS (Version 26.0). Continuous variables were expressed as mean ± SD, and categorical variables as

frequencies and percentages. Student's t-test, Chi-square test, and one-way ANOVA were used. Statistical significance was set at $p<0.05$.

## RESULTS

### Serum HGF levels

There was a significant increase in preoperative serum HGF levels of invasive ductal carcinoma patients as compared to benign breast disease and normal women. Serum HGF levels obtained among carcinoma patients was in the range of 936-2731pg/ml, mean value being 1386pg/ml as compared to benign breast diseases with a range of 726-1556pg/ml, mean value =944pg/ml and normal samples ranged 160-481pg/ml, mean value=337g/ml. The p value is <0.001 which shows statistical significance in the present study.

### SERUM HGF VALUES:

Serum HGF values in Invasive duct carcinoma was in the range of 936-2731pg/ml with a mean of 1386pg/ml.and other values as depicted in the Table 1 The p value is <0.0001 which shows statistical significance in the present study.

**Table 1: SERUM HGF VALUES**

| Category | No of cases | Serum HGF pg/ml (range) | Mean value (pg/ml) | p-value |
|---|---|---|---|---|
| Invasive duct carcinoma | 35 | 936–2731 | 1386 | |
| Benign breast disease | 9 | 726–1556 | 944 | <0.0001 |
| Normal serum samples | 8 | 160–481 | 337 | |

### HORMONAL RECEPTOR STATUS -ER, PR AND HER-2/NEU EXPRESSION

Out of 35 cases, IHC was done in 25 cases. The results are as shown in Table 2

**Table 2: DISTRIBUTION OF CASES ACCORDING TO ER, PR AND HER2 NEU EXPRESSION**

| IHC | Positive | Percentage | Negative | Percentage |
|---|---|---|---|---|
| ER | 20 | 80 | 05 | 20 |
| PR | 18 | 72 | 07 | 28 |
| Her2neu | 11 | 44 | 14 | 56 |

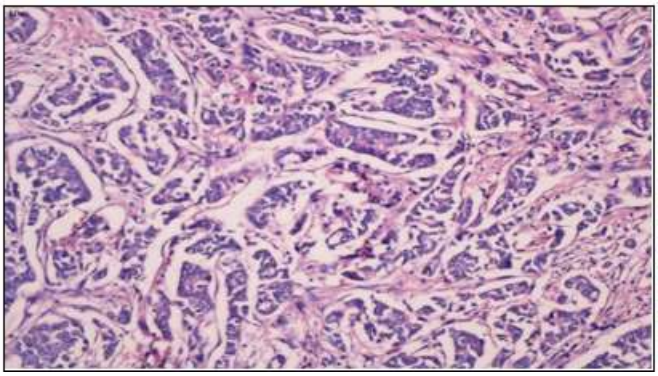

**Figure 1: Invasive breast carcinoma**

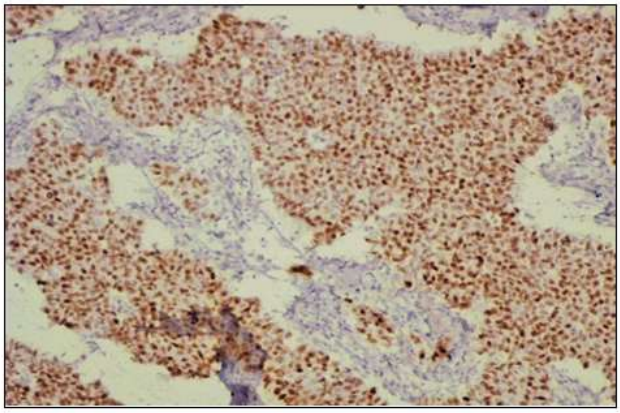

**Figure 2:ER POSITIVE: Tumor cells showing nuclear positivity with estrogen receptor immunostain**

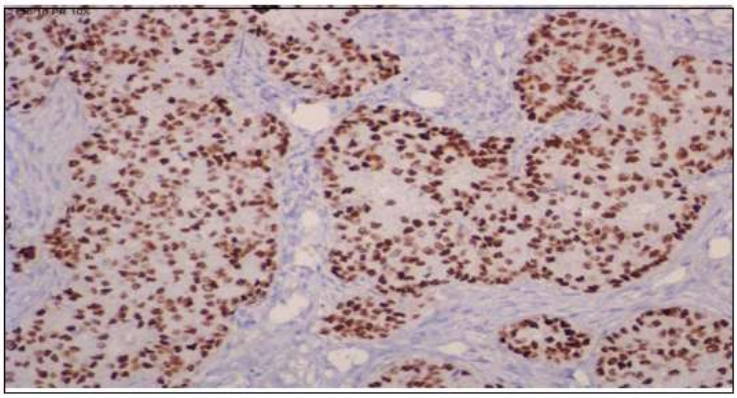

**Figure 3: PR POSITIVE- Tumor cells showing nuclear positivity with progesterone receptor immunostain.**

## DISCUSSION

There was a significant increase in preoperative serum HGF levels of invasive ductal carcinoma patients as compared to benign breast disease and normal women. Serum HGF levels obtained among carcinoma patients was in the range of 936-2731pg/ml, mean value being 1386pg/ml as compared to benign breast diseases with a range of 726-1556pg/ml, mean value =944pg/ml and normal samples ranged 160-481pg/ml, mean value=337g/ml. The p value is <0.001 which shows statistical significance in the present study. While assessing the Association of ER, PR AND Her2Neu with serum hgf levels and comparison of p-values with other studies The present study showed no signficant correlation between ER, PR, HER2Neu positive tumors with serum HGF levels. In some of the earlier studies association were found with only ER expression.[16,17] The level of the HGF receptor, cMet is negatively correlated with ER status.[14] Table No 03 show p-values and comparison with other studies-

**Table 3: p- values of ER,PR AND HER2Neu expression and comparison with other studies**

| IHC | H A Attar et al[59] | H H Ahmed et al.[52] | SMS Chen et al.[58] | Present study |
|---|---|---|---|---|
| ER | 0.262 | 0.039 | 0.035 | 0.799 |
| PR | 0.89 | 0.97 | – | 0.680 |
| Her2Neu | – | – | – | 0.052 |

There is a significance association between therapeutic and prognostic response with the molecular subtypes. Luminal A subtype has the best overall prognosis and survival and can be managed with hormonal agents alone. Luminal B tumours which often exhibit HER2 amplification have a prognosis worse than that of luminal A carcinomas and may benefit from standard chemotherapy. The subtype with the worst prognosis is basal-like tumour, which is characterized by Triple-negative status and expression of CK 5/6, EGFR, and c-kit. These patients do not have the advantage of Herceptin/ hormonal therapies/ conventional chemotherapy. Overall, these subgroups are heavily driven by ER, HER2neu and proliferative activity; the features that are easily and relatively inexpensively assessed on formalin-fixed paraffin-embedded tissue samples with the use of IHC. Therefore, in place of inaccessible and expensive molecular profiling, IHC can be used to determine the molecular subtypes with sufficient accuracy, thereby improving our ability to determine the appropriate treatment and prognosis of each tumour.[18]

Hormonal receptors including ER, PR, and HER2/neu are well-established predictive and prognostic biomarkers that guide treatment selection. The limitations of this study include its relatively small sample size and single-center design. Larger multicenter studies are warranted to validate serum HGF as a prognostic biomarker and therapeutic target.

## CONCLUSION

HGF known to be identical to scatter factor plays an important role in various stages of cancer progression including cell proliferation, movement, invasiveness, morphogenesis, and angiogenesis. The present study was a descriptive type of study conducted at JSS hospital, Mysuru. Preoperative serum HGF estimation was done in 35 cases of invasive ductal carcinoma using sandwich ELISA assay which were compared with benign breast disease and normal samples as controls. The study showed a significant increase in serum HGF levels in invasive ductal carcinoma as compared to benign breast disease and normal samples and there was statistical significance. This was comparable with various previous studies . The increase in HGF could be explained by overstimulation of the cells that secrete HGF through autosecretion or mutation and aberrant regulation of the HGF/cMet signalling pathway or an imbalance between HGF activators and inhibitors. Serum HGF levels were correlated with known prognostic factors. IHC was done in 25 cases, ER, PR, HER2Neu was positive in 80%,72% and 44% of the cases respectively Serum HGF levels were elevated in all breast carcinoma patients. These findings suggest that serum HGF may be a useful non-invasive biomarker for identifying aggressive disease and could have prognostic and therapeutic implications.

## REFERENCES

1. Mallath MK, Taylor DG, Badwe RA, Rath GK, Shanta V, Pramesh CS et al. The growing burden of cancer in India: epidemiology and social context. TheLancet Oncology. 2014;15(6):e205-12.
2. Parkin D M, Bray F, Ferlay J, and Pisani P. Global cancer statistics. Ca-A Cancer Journal for Clinicians.2005; 55: 74–108
3. Colzani E, Liljegren A, Johansson AL, Adolfsson J, Hellborg H, Hall PF et al. Prognosis of patients with breast cancer: cause of death and effects of time since diagnosis, age, and tumor characteristics. J Clin Oncol. 2011;29(30):4014-21
4. Faratian D. Systems pathology. Breast Cancer Res. 2010 Dec 20;12 Suppl 4:S4.
5. 5)Stankov A, Bargallo-Rocha JE, Silvio A, Ramirez MT, Stankova-Ninova K, Meneses-Garcia A. Prognostic factors and recurrence in breast cancer: experience at the national cancer institute of Mexico. ISRN oncology. 2012 Jul 5;2012.
6. Boyle P. Triple-negative breast cancer: epidemiological considerations and

recommendations. Ann Oncol. 2012;23 Suppl 6:vi7-12.
7. Funakoshi H, Nakamura T. Hepatocyte growth factor: from diagnosis to clinical applications. Clinica chimica acta. 2003 Jan 1;327(1-2):1-23.
8. Parr C, Watkins G, Mansel RE, Jiang WG. The Hepatocyte growth factor regulatory factors in human breast cancer. Clinical cancer research.2004;10:202-11.
9. Dabbs DJ. Breast Pathology E-Book. Elsevier Health Sciences; 2016 Nov 4.
10. Rosen PP, Hoda SA, Brogi E, Koerner FC. Rosens breast pathology. Philadelphia: Wolters Kluwer Health; 2014.
11. Battifora H, Gaffey M, Esteban J, Mehta P, Bailey A, Faucett C, Niland J. Immunohistochemical assay of neu/c-erbB-2 oncogene product in paraffin- embedded tissues in early breast cancer. Retrospective follow-up study of 245 stage I and II cases. Mod Pathol 1991, 4: 466–474.
12. Muss HB, Thor AD, Berry DA, Kute T, Liu ET, Koerner F, Cirrincione CT, Budman DR, Wood WC, Barcos M, et al. c-erbB-2 expression and response to adjuvant therapy in women with node-positive early breast cancer. N Engl J Med 1994, 330: 1260–1266
13. Fitzgibbons PL, Dillon DA, Alsabeh R, Berman MA, Hayes DF, Hicks DG, et al. Template for reporting results of biomarker testing of specimens from patients with carcinoma of the breast. Arch Pathol Lab Med. 2014 May;138(5):595-601.
14. Greenberg R, Schwartz I, Skornick Y, Kaplan O. Detection of hepatocyte growth factor/scatter factor receptor (c-Met) in axillary drainage after operations for breast cancer using reverse transcriptase–polymerase chain reaction. Breast Cancer Research. 2003 Jun;5(3):R71
15. El-Attar HA, Sheta MI. Hepatocyte growth factor profile with breast cancer. Indian J PatholMicrobiol2011;54(3):509-13.
16. Ahmed HH, Metwally FM, Mahdy ES, Shosha WG, Ramadan SS. Clinical value of serum hepatocyte growth factor, B-cell lymphoma-2 and nitric oxide in primary breast cancer patients. Eur Rev Med Pharmacol Sci. 2012 Jul1;16(7):958-65.
17. Sheen-Chen SM, Liu YW, Eng HL, Chou FF. Serum levels of hepatocyte growth factor in patients with breast cancer. Cancer Epidemiol Biomarkers Prev2005;14(3):715-7.
18. Koka R, Ioffe O. Breast carcinoma: Is molecular evaluation a necessary part of current pathological analysis?. Seminars in Diagnostic Pathology.