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LETTERS

Unveiling the effect of Inflammatory Cytokines TNF-α, IL-6, and IL-1β in Breast Cancer prevalence and progression

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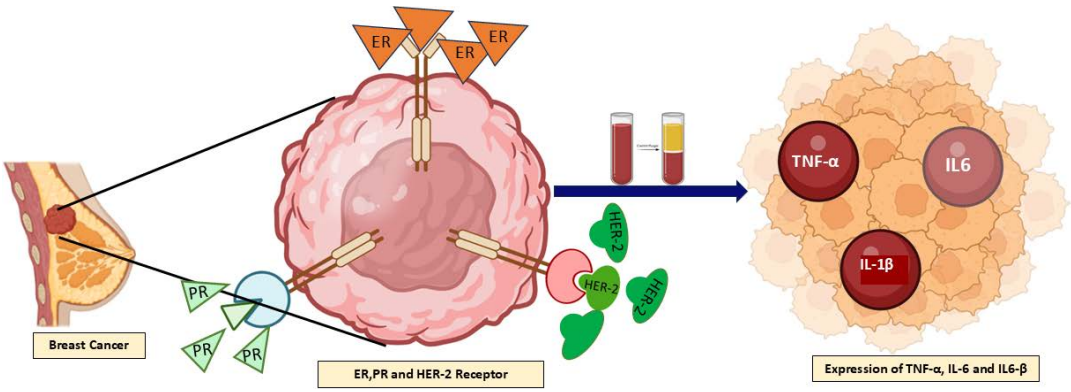
Article

ABSTRACT



Breast cancer remains a leading cause of cancer-related morbidity and mortality among women globally. Breast cancer is the most diagnosed cancer in women. Metastasis is the primary cause of mortality for breast cancer patients. In Bihar, there are so many cases of Breast Cancer patients found but most of them collected near the Gangetic plane. Also, we compared the real data of Breast cancer patients from the data available on TCGA. We performed comparison of the trend of ER, PR, and HER-2 expression trend in both data. This research has highlighted the significant role of inflammatory cytokines in the tumor microenvironment, particularly tumor necrosis factor-α (TNF-α), Interleukin-6 (IL-6), and Interleukin-1 beta (IL-1β). These cytokines are implicated in various stages of breast cancer development, including tumor initiation, progression, and metastasis. TNF-α helps to promote tumor growth through enhancing processes such as angiogenesis and inhibition of apoptosis. IL-6 and IL-1β contribute to cancer cell proliferation, survival, and resistance to therapy by activating key signaling pathways like the JAK/STAT pathway. This research reveals the roles of TNF-α, IL-6, and IL-1β in breast cancer, and sheds light on how they affect the tumor microenvironment and the course of the illness. These cytokines contribute to breast cancer progression and may help to produce targeted therapy and open up new options for individualized treatment plans.

Keywords: Breast cancer, Cytokines, TNF-α, IL-6, and IL-1β, Estrogen, Progesterone, Human Epidermal Growth Factor-2

INTRODUCTION

The most common cancer diagnosed worldwide is breast cancer, and during the past few decades, the mortality rate of this disease has increased. This article highlights at estimates for 2040 and the global burden of breast cancer in 2020.[1,2] The pathophysiology of breast cancer involves multiple variables like age, lifestyle, genetics, modifications, tumour size, involvement of axillary nodes, histologic grade, and hormone receptor status.[3] These variables influence treatment decisions and patient prognosis.[4] According to estimates, 685,000 women died from this serious condition of breast cancer in 2020, making up 16% of all female cancer deaths. Before this, there was a lack of adequate public health response to this trend, which is why the World Health Organization (WHO) launched the Global Breast Cancer Initiative. WHO and other broad organizations lower the death rate from breast cancer by promoting early detection, Appropriate treatment, and patient management. For this, the organization enlists the help of international organizations and organizes long-term initiatives to enhance results. The illness burden must be a strong reason for this worldwide trend and variances in the illness burden.[5] Death rate of breast patient has been increased in recent days.[6] The immunomodulatory proteins known as cytokines are generated by stromal, endothelial, and immune cells. They serve as regulators for immune cell development, maturation, and responsiveness and are involved in cell communication during inflammation.[7] Tumour necrosis factor-α (TNF-α) is a multifunctional cytokine that has roles in pro-angiogenic, survival, apoptotic, necrotic, and inflammation. Activated macrophages, natural killer (NK) cells, and T cells are

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the main cells that express it; many other cells also do so in smaller quantities. Tumor necrosis factor-α (TNF-α) is an inflammatory cytokine that can produce more than one effect, regulating immune responses, survival, and apoptosis among other cell.[8] It plays a significant role in carcinogenesis in the relationship between inflammation and the development of tumor. However, understanding of the underlying mechanism is still lacking. However, TNF-α can trigger breast cancer cells to over-regulate HBXIP and by attaching to its receptors, TNF-α may encourage the production of growth factors, proteases, and cytokines, such as TNF-α receptor 2 (TNFR2) and TNF-α receptor 1 (TNFR1). While TNFR1 is widely expressed in human tissues and acts as a key TNF-α signalling receptor, TNFR2 is expressed restrictedly in immune cells and mediates specific biological functions.[9] Mechanism is still unclear of overexpression, if TNF-α but it is found that it can increase the expression of its receptors while tumor progessrion.[10] TNF-α, an inflammatory agent, can encourage the development, invasion, metastasis, and lymph angiogenesis of cancer.[7] In response to the activation of TNFR-associated death domain protein (TRADD), nuclear factor kappaB (NF-κB) mediated the recruitment of protein complex leads to cell survival and release of inflammatory mediators.[11] Innate immunity and inflammation are balanced by the action of NF-κB, a crucial regulator. Studies have shown that activation of TNFR1 can cause canonical or noncanonical transcription regulation of genes producing pro-inflammatory and pro-survival molecules in most cell types via NF-κB.[12] Squamous cell proliferation in other cancers is aided by TNFR1-mediated NF-κB activation. TNF-α-induced cytokine production is enhanced by the combined effects of NF-κB and p38/MAPK signalling.[13] Initiating signalling cascades to support cell development, differentiation, proliferation, and response to inflammation or stress is what phosphokinase p38 does, just like other members of the MAPK family. The nucleus receives signals from cytokine receptors through the medium of the signal transducer and activator of transcription 3 (STAT3).[14] A number of oncogenic signalling pathways in malignancies converge at the constitutive activation of STAT3. Under TNF-α injection, TNFR1 activates the canonical or non-canonical NF-κB pathway and subsequently triggers the IL-6/JAK1,2/STAT3 signalling state.[15] It is unclear, though, what role TNF-α plays in controlling TNFR1/NF-κB (and/or p38)/p-STAT3 in breast cancer. The most prevalent malignancy in women to receive a diagnosis is breast cancer. Patients with breast cancer die primarily from metastasis. Breast cancer metastatic dissemination is caused by a variety of pathways, one of which is the signalling system mediated by interleukin-6 (IL-6).[16] The pleiotropic cytokine IL-6 is involved in numerous physiological processes, such as immune surveillance, bone remodelling, metabolism, acute inflammation, and cell proliferation.[17] A signal-transducing hexametric receptor complex is formed when IL-6 attaches to the IL-6 receptor (IL-6Rα), which then attaches to the glycoprotein 130 (gp130) receptor.[18] Recruitment and activation of Janus kinases (JAKs) occurs; active JAKs then phosphorylate signal transducers and activators of transcription 3 (STAT3) to initiate gene regulation.[11] A vicious inflammatory cycle is promoted by constitutively active IL-6/JAK/STAT3 signalling, which promotes cancer cell proliferation and invasiveness while inhibiting apoptosis.[19] STAT3 also amplifies IL-6 signalling. Autophagy is possible through several mechanism to induced apoptosis.[20] A poor clinical prognosis and metastasis are linked to aberrant production of IL-6, which is seen in a variety of cancer types.[19] Various treatments are presently being assessed in preclinical and clinical settings for the treatment of breast cancer. The IL-6 pathway is often active in breast cancer, which can both stimulate the disease's spread and inhibit the immune system's ability to fight the tumor.[21] The IL-6 pathway's constituents, including gp130 receptor, JAKs, STAT3, IL-6, and IL-6Rα. Numerous IL-6 pathway components are interesting targets because of their significant roles in human malignancies.[22] Treatment approaches that target gene as well as the current scientific understanding of the IL-6 signalling system and its role in breast cancer metastasis. Variety of cytokines and trend of hormonal level change can be beneficial to know the reason behind increasing number of Breast cancer patient.[23] We can consider increased cytokines a therapeutic biomarker in future.[24] This research provide insight in to ER (Esterogen), PR (Progesterone, HER2 (Human Epidermal Growth Factors-2) trend in real data of hospital patients from several regions in Bihar and c-BioPoral of breast cancer. Also analysed the level of TNF-α, IL-6 and IL-1β in breast cancer patient.

MATERIAL AND METHODS

With a total size of 94,163 Km^2, Bihar, a state in northeastern India, is the 12th largest in the nation. The third state, with an estimated population of 104 million, where 11.29 % live in urban administration, it is divided into 38 districts, 534 subdistricts or blocks, 101 subdivisions, and nine divisions. The Ganga River divides the state approximately evenly into north and south Bihar.[25] Here, in this study patients were admitted to the hospital and then samples of location were noted during the visit and latitude and longitude of location were observed. This study included 220 random breast cancer patients of Mahavir cancer Shanshan and Research Centre Patna. Breast cancer was confirmed by the histopathological examination. The inclusion criteria for this study were: females (not pregnant) and Male between 0 and 100 years of age, confirmed breast cancer patients (based on medical reports), had no major comorbidities. The clinicopathological characteristics of breast cancer patients including the molecular subtyping, histopathological type, grade, stage of the disease, and the expression of reproductive hormones ER, PR, and the epidermal growth receptor HER2 were obtained from the patient's medical records. Also, 31 patients for TGF-α, IL-6 and IL-1β analysis.

c-BioPortal

The Cancer Genome Atlas (TCGA, Pan-Cancer) multi-omics data was obtained and examined via the Cancer Genomics Portal (c-BioPortal), an online resource for cancer genomics data (http://www.cbioportal.org). 160 samples of breast cancer (BC) from c-BioPortal were screened for inclusion using the following criteria: the datasets had to be female or male include data, and

specify cancer subtypes based on the ER, PR, and HER2 receptors. We analyzed the data using Python Jupiter Notebook.

Data Acquisition and Preprocessing

Data Retrieval:

Obtained data from Mahavir Cancer Shanshan and Research Centre Patna and public repositories c-BioPortal.

Data Cleaning and Visualization:

- Removed missing values.
- Normalize expression data for log transformation and quantile normalization) to correct for technical variability.[26]

```
import pandas as pd
import matplotlib.pyplot as plt
#Plot level distributions
import pandas as pd
import matplotlib.pyplot as plt
import seaborn as sns
#Load data from a CSV file
data = pd.read_csv('mahavir_data.csv')
#Inspect the first few rows of the Data Frame
print(data.isnull().sum())
#Drop or fill missing values as needed
data = data.dropna()  # or data.fillna(value)
# Plot a histogram for a specific column
plt.figure(figsize=(10, 6))
plt.hist(data['column_name'],bins=, alpha=, color='')
plt.title('Histogram of Column Name')
plt.label('Frequency')plt.grid(True)plt.show()
```

Ethical Approval

As evidenced by the approved IEC No. MCS/Research/2019-2020/11, the research project was approved by the Ethics Committee (IEC) of the Mahavir Cancer Sansthan and Research Centre.

Blood Sample Collection

Blood was collected from the peripheral vein of donors into 6-ml BD Vacutainer Clot Activator tube.[25] The acquired blood samples were analysed using the standard protocols in order to analyze six independent standard series, evaluation of the deviation of the TNF-α, IL-6 and IL-1β concentration in patients with ICH, standard addition and visual analysis of whole UV-Visible spectra were carefully performed.

RESULTS

Sample location and stage-wise prevalence of Breast Cancer patients have been shown in figure 1. Our analysis of breast cancer patient data from various regions in Bihar revealed significant geographical disparities in the incidence of advanced-stage disease, particularly stage 4, as mentioned in the figure 1. The study focused on identifying regional hotspots where stage 4 breast cancer cases were notably high, with a specific emphasis on the areas near Vaishali, Patna, and the Gangetic plains. The results indicated that the incidence of stage 4 breast cancer in the regions near Vaishali, Patna, and the Gangetic plains was significantly higher compared to other areas in Bihar. Especially, the data showed that increased population of breast cancer patients in these regions were diagnosed at stage 4, compared to the overall average percentage for the rest of Bihar.

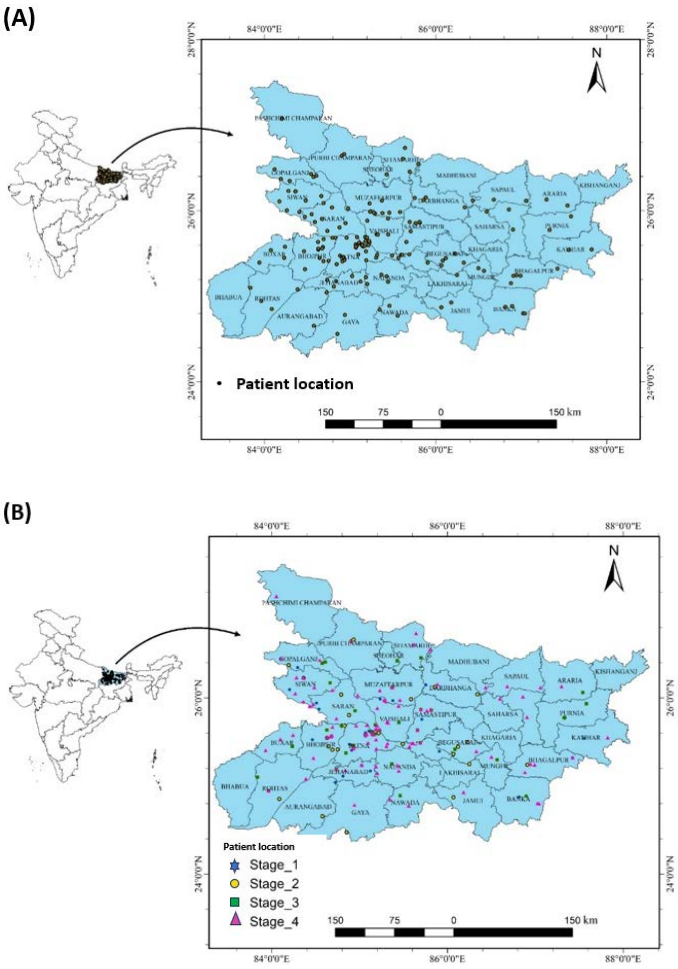

Figure 1: (A) Distribution of Breast Cancer patients in different parts of Bihar. The prevalence of breast cancer patients is high around all the areas of Bihar, more patients were from the gigantic plane area. **(B)** Stagewise distribution shows these patterns where, stage 4 stage was followed by stage 2, stage 3, and stage 1.

The regions with the lowest incidence of stage 4 breast cancer included Araria, Purnia, Aurangabad and Banka. Our findings also highlighted patients from the high-incidence areas near Vaishali, Patna, and the Gangetic plains tended to present with larger tumors and more extensive metastasis at the time of diagnosis.

In our analysis of breast cancer patients, elevated levels of TNF-α (Tumor Necrosis Factor--α), IL-6 (Interleukin-6), and IL-1β (Interleukin-1β) were observed to correlate with adverse clinical parameters and outcomes. As mentioned in the figure 6, the observation of TNF-α test sample value was higher than 24 pg/ml.[27] As mentioned in the figure 7, in the case of IL-6, we got an increased level of test sample when it comes to the normal range (less than 5.186 pg/ml).[28] Also, in the case of IL-1β, we got an increased level of test samples in comparison to the normal

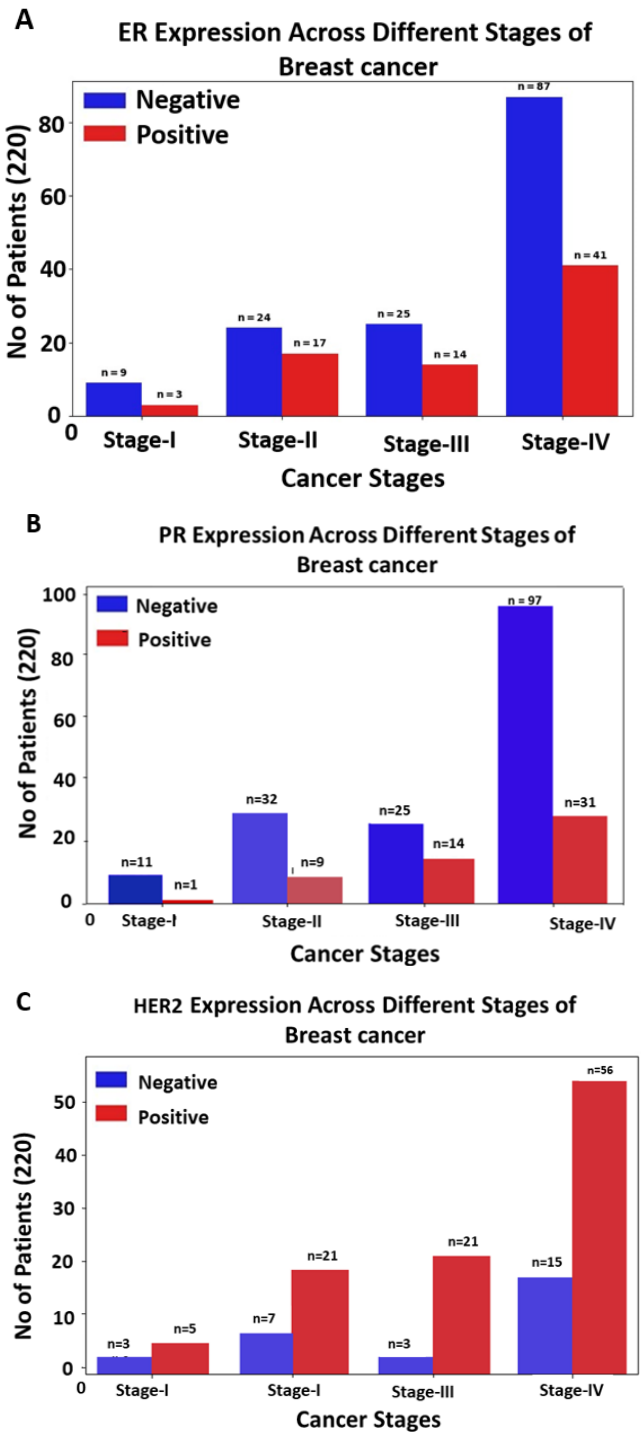

Figure 2: **(A)** ER expression of breast cancer patients in different stages across Bihar. Collected data showed the distribution of patient samples for Estrogen (ER) found among different stages. Here, more ER-negative patient found in all stages of the patient. **(B)** PR expression of breast cancer patients in different stages across Bihar. Collected data showed the distribution of patient samples for Progestogen (PR) found among different stages. Here, more PR-negative patient found in all stages of the patient. **(C)** We compared these data with the data of c-BioPortal. HER-2 expression of breast cancer patients in different stages across Bihar. Collected data showed the distribution of patient samples for Human Epidermal growth factor (HER-2) found among different stages. Here, more HER-2-positivepatients in all stages of the patient.

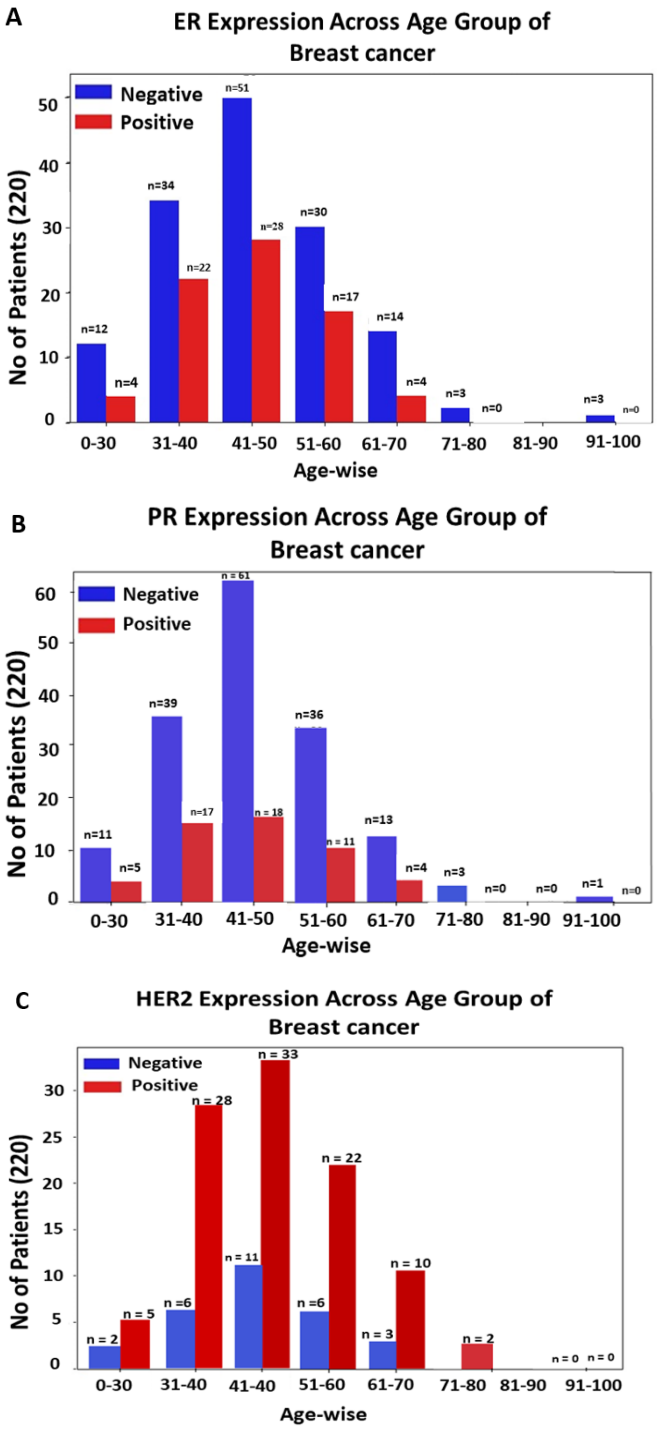

Figure 3: ER expression of breast cancer patients in different Age groups across Bihar. **(A)** Collected data showed the distribution of patient samples for Human Estrogen (ER) found among different stages. Here, more ER-negative patients found in all stages of the patient. **(B)** PR expression of breast cancer patients in different Age groups across Bihar. Collected data showed the distribution of patient samples for Human Progestogen (PR) found among different age group. Here, more ER-negative patients found in all stages of the patient. **(C)** HER-2 expression of breast cancer patients in different Age groups across Bihar. Collected data showed the distribution of patient samples for Human epidermal growth (HER-2) found among different stages. Here, more ER-positive patients found in different age group of the patient.

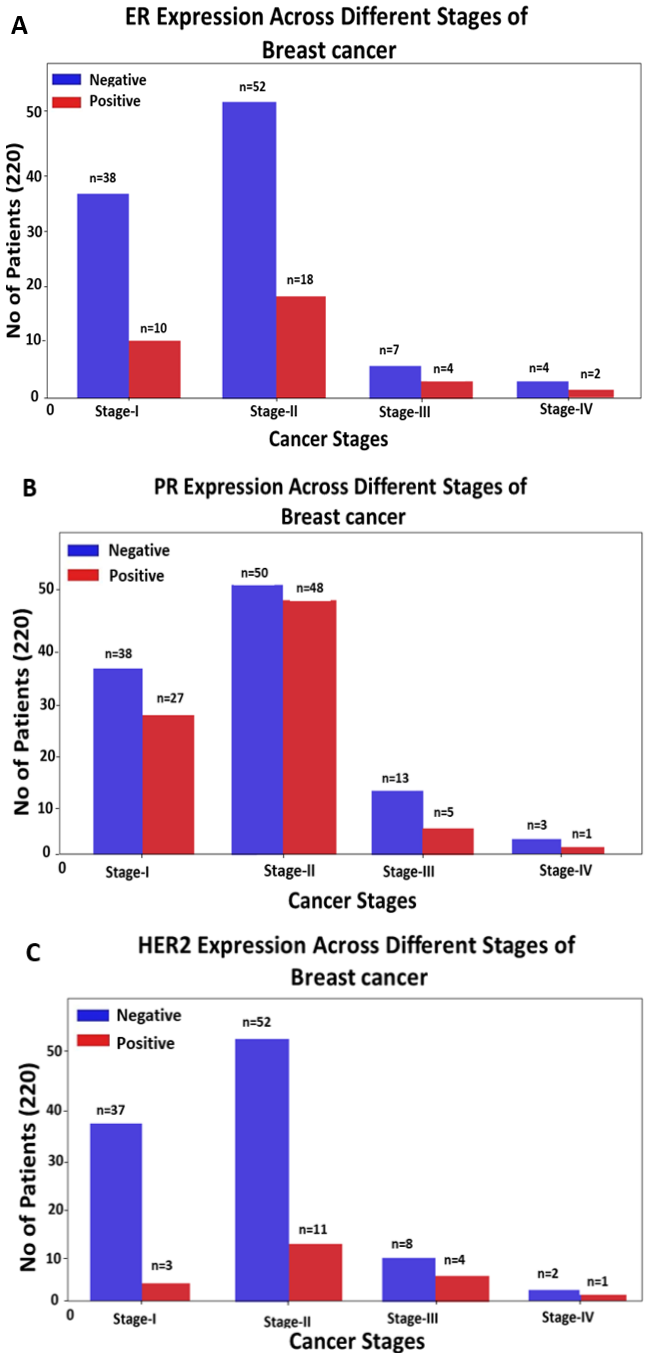

Figure 4: Collected data from c-BioPortal showed the level of patient samples for Estrogen (ER) found among different stages. Here, more ER-positive patients in all stages found in patients. Collected data from c-BioPortal showed the distribution of patient samples for Estrogen (ER) found among different stages. Here, more ER-positive patient found in all stages of the patient. Collected data from c-BioPortal showed the distribution of patient samples for Human Epidermal growth factor (HER-2) found among different stages. Here, more HER-2 negative patients found in all stages.

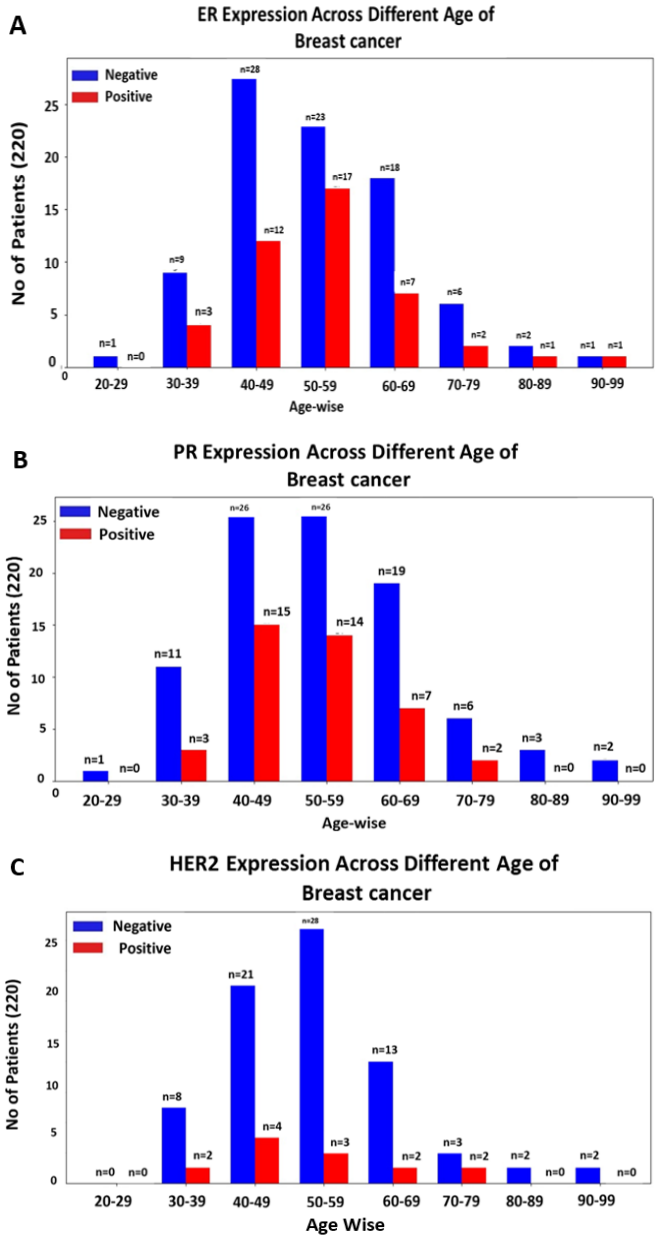

Figure 5: Collected data from c-BioPortal showed the distribution of patient samples for Estrogen (ER) found among different stages. Here, more ER-Negative patients found in all stages of the patient. Collected data from c-BioPortal showed the level of patient for Progesterone (PR) found among different stages. Here, more PR-Negative patients found in all stages of the patient. Collected data from c-BioPortal showed the distribution of patient samples for Human epidermal growth factor (HER-2) found among different stages. Here, more HER-2 Negative patients found in all four stages of the patient. The analysis of ER (Estrogen Receptor), PR (Progesterone Receptor), and HER-2 (Human Epidermal Growth Factor Receptor 2) statuses in the hospital emergency room (ER) setting revealed significant findings regarding their distribution and prevalence trends. In our hospital cohort, the distribution of breast cancer subtypes based on receptor status showed that patients were ER-Negative, PR-Negative, and HER-2-positive as mentioned in the figure 2 and 3. These populations closely mirrored the trends observed in the c-BioPortal database, where some of the cases were reported as ER-negative, PR-negative, and HER-2 negative.

Statistical analysis indicated a high degree of similarity between our hospital data and the c-BioPortal dataset in terms of ER, and PR, but it varies in terms case of HER-2 status distributions as mentioned in the figure 4 and 5. Specifically, the proportion of ER-negative and PR-negative cases in our hospital cohort was statistically comparable to the data reported in c-BioPortal, suggesting consistency in the prevalence of hormone receptor-positive breast cancers across different datasets. Similarly, the prevalence of HER-2-positive cases in our hospital cohort is not aligned closely with the figures reported in c-BioPortal, indicating robust concordance in the representation of HER-2-positive breast cancer cases. These results underscore the reliability of c-BioPortal as a representative resource for understanding the molecular characteristics and epidemiology of breast cancer subtypes. The findings also highlight the utility of integrating local clinical data with large-scale genomic databases to enhance the accuracy and generalizability of research findings in breast cancer. However, it is important to note that the specific demographics and characteristics of our hospital patient population limit our study. Future research should aim to validate these findings across diverse populations and clinical settings to strengthen further our understanding of breast cancer epidemiology and subtype distribution.

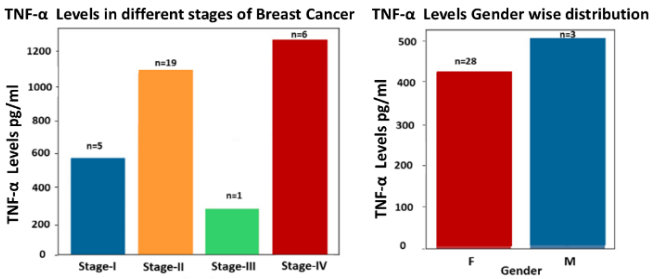

Figure 6: Increased level of TNF-α in Breast Cancer patient samples found stagewise and gender-wise. In 4 stages of Breast Cancer sample values are higher than 24 pg/ml (picogram per milliliter). In both gender TNF-α was increased, but in male it is also found increased as compare to female.

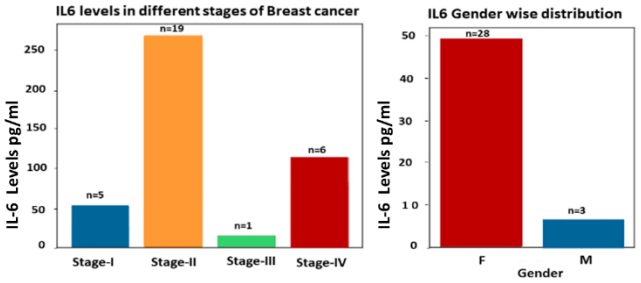

Figure 7: Analysis of IL-6 in Breast Cancer patient samples for and ere we found an increased level of IL-6 in stagewise and gender-wise. Increased level of IL-6 found in the sample Breast cancer patients as compare to normal range (less than 5.186 pg/ml).

range (less than 10 pg/ml) as mentioned in the figure 8. These results collectively highlight the potential prognostic value of TNF-α, IL-6, and IL-1β as biomarkers in triple negative and triple positive breast cancer as mentioned in the figure 9. They also understand the therapeutic potential of targeting these cytokines and their signaling pathways to improve treatment outcomes and patient survival. Further prospective studies are warranted to validate these findings and explore the mechanistic implications of cytokine dysregulation in breast cancer progression.

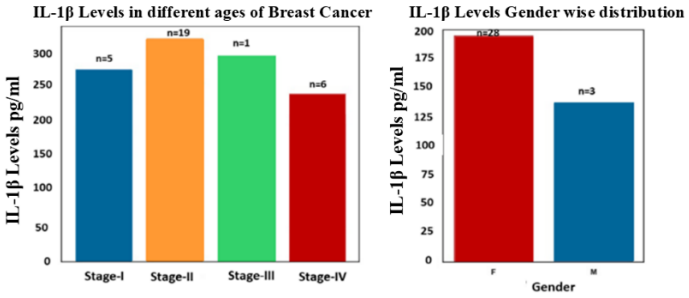

Figure 8: Analysis of IL-1β in Breast Cancer patient samples for and here we found an increased level of IL-1β in stagewise and gender-wise. Increased level of IL-1β found in the sample Breast cancer patients.

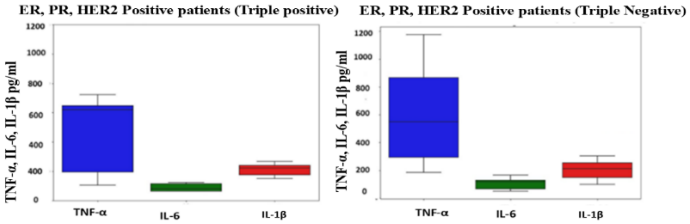

Figure 9: Analysis of TNF-α, IL-6and IL-1β in Breast Cancer patient samples. Here, we found an increased level of TNF-α, IL-6 and IL-1β in Triple positive Breast Cancer patients. Analysis of TNF-α, IL-6 and IL-1β in Breast Cancer patient samples for and here we found an increased level of TNF-α, IL-6 and IL-1β in Triple Negative Breast Cancer patients.

Discussion

Analysis of breast cancer patient data from various regions in Bihar revealed significant geographical disparities in the incidence of advanced-stage disease, particularly stage 4. The study focused on identifying regional hotspots where stage 4 breast cancer cases were notably high, with a specific emphasis on the areas near Vaishali, Patna, and the Gangetic plains. The results indicated that the incidence of stage 4 breast cancer in the regions near Vaishali, Patna, and the Gangetic plains was significantly higher compared to other areas in Bihar.[29] Specifically, the data showed breast cancer patients in these regions were diagnosed at stage 4, compared to the overall average population of the rest of Bihar.[30] The significant increase in the data were substantially higher than those observed in other parts of Bihar, where the incidence of stage 4 breast cancer.[31] The analysis of ER (Estrogen Receptor), PR (Progesterone Receptor), and HER-2 (Human Epidermal Growth Factor Receptor 2) statuses in the hospital emergency room (ER) setting revealed significant findings regarding their distribution and prevalence trends.[32] Specifically, the proportion of ER-negative and PR-negative cases in our hospital cohort was statistically comparable to the data reported in c-BioPortal suggesting consistency in the prevalence of hormone receptor-positive breast cancers across

different datasets.[33] Similarly, the prevalence of HER-2 positive cases in our hospital cohort aligned closely with the figures reported in c-BioPortal, indicating robust concordance in the representation of HER-2-negative breast cancer cases.[34] The analysis of TNF-α (Tumor Necrosis Factor- α), IL-6 (Interleukin-6), and IL-1β (Interleukin-1 beta) levels in breast cancer patients has provided insights into their potential roles in disease progression and prognosis.[35,36] This study focused on correlating the expression levels of these inflammatory cytokines with clinical outcomes in breast cancer patients, aiming to elucidate their significance in the context of tumor biology and patient management. The trend of this findings revealed notable associations between elevated levels of TNF- α, IL-6, and IL-1β and adverse clinical parameters in breast cancer.[37] Elevated TNF-α levels correlation with more aggressive tumor characteristics, including larger tumor size, higher histological grade, and increased incidence of lymph node metastasis.[38] TNF-α pro-inflammatory properties promote tumor cell survival, angiogenesis, and resistance to apoptosis, contributing to tumor progression and metastasis. Similarly, elevated levels of IL-6 and IL-1β were associated with poorer clinical outcomes in breast cancer patients.[39] IL-6 and IL-1β are known to promote cancer cell proliferation, survival, and invasion through activation of the JAK/STAT signaling pathway and other pro-survival pathways. Our analysis found that higher IL-6 and IL-1β levels correlated with advanced disease stage, poorer response to treatment, and decreased overall survival rates among breast cancer patients.[41] Furthermore, the interplay between these cytokines and hormone receptor status in breast cancer adds another layer of complexity.[40] Elevated TNF-α, IL-6, and IL-1β levels were often observed in hormone receptor-negative breast cancers, which are generally associated with more aggressive clinical behavior and poorer prognosis compared to hormone receptor-positive subtypes. The implications of these findings are significant for clinical practice and therapeutic strategies. Targeting TNF-α, IL-6, and IL-1β signaling pathways presents opportunities for developing novel therapeutic interventions aimed at suppressing inflammation-driven pathways in breast cancer. Strategies such as targeted monoclonal antibodies, small molecule inhibitors, and immunomodulatory agents that inhibit TNF-α or IL-6 signaling pathways could potentially improve treatment outcomes and patient survival.[41] Analysis underscores the potential prognostic and therapeutic significance of TNF-α, IL-6, and IL-1β in breast cancer.[42] Elevated levels of these cytokines are associated with aggressive tumor behavior and poorer clinical outcomes, suggesting their utility as biomarkers for patient stratification and as targets for novel therapeutic interventions in breast cancer management. There are so many factors Continued research in this area holds promise for advancing personalized treatment approaches and improving outcomes for breast cancer patients. This alignment supports the use of c-BioPortal as a valuable tool for breast cancer research and underscores the potential for leveraging integrated clinical-genomic data to advance personalized treatment strategies and improve patient outcomes.

Conclusion

In conclusion, our results indicate a significant geographic disparity in the incidence of stage 4 breast cancer within Bihar, with regions near Vaishali, Patna, and the Gangetic plains exhibiting a markedly higher prevalence of advanced-stage disease. These findings underscore the need for targeted interventions in these areas to improve early detection and reduce the burden of late-stage breast cancer. Our results demonstrate that the distribution and prevalence trends of ER, PR, and HER-2 statuses in our hospital ER setting closely match those observed in the c-BioPortal database. This alignment supports the use of c-BioPortal as a valuable tool for breast cancer research and underscores the potential for leveraging integrated clinical-genomic data to advance personalized treatment strategies and improve patient outcomes. Increased levels of cytokines are strong indicators of malignancy.

Limitation

However, it is important to note that the specific demographics and characteristics of our hospital patient population limit our study. Future research should aim to validate these findings across diverse populations and clinical settings to strengthen further our understanding of breast cancer epidemiology and other analyses. However, it is important to acknowledge the limitations of our study. The analysis was retrospective, relying on archived clinical data, which may introduce biases and limit the generalizability of findings. Future prospective studies incorporating larger patient cohorts and longitudinal assessments of cytokine levels are warranted to validate these associations and elucidate the mechanistic underpinnings of TNF-α, IL-6, and IL-1β in breast cancer progression.

Data Availability

The datasets used and/or analyzed during the current study are available from the Mahavir Centre Santhan and Research Centre Patna reasonable request.

Acknowledgments

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Conflict of Interest Statement

Authors declare that there is no conflict of interest

Abbreviations

ER: Estrogen Receptor
PR: Progesterone Receptor
HER-2: Human Epidermal Growth Factor Receptor-2
TNF- α: Tumor Necrosis Factor- α
IL-6: Interleukin-6
ILβ-1β: Interleukin 6-1β

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