To evaluate the role of Neutrophil to Lymphocyte Ratio (NLR) as a Prognostic Marker of Breast Cancer

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Abstract

Breast cancer is one of the most prevalent cancers in females not only in India but worldwide and is being increasing at an alarming rate. Despite early diagnosis and therapeutic advances having considerably reduced mortality, there is still need for more specific biomarkers for early detection as well as for prognosis and biomarker for monitoring treatment response.

In this regard, Neutrophil to Lymphocyte ratio (NLR) values have been shown to mirror the tumor-induced inflammatory status and have been demonstrated to be a reliable prognostic tool across stages of disease and therapeutic approaches. The NLR may allow to further stratify patients with different outcomes of deriving a significant clinical benefit. However, despite its accessibility, low cost, and easy interpretation, the NLR is still poorly used as a prognostic tool in daily clinical practice.

The neutrophil to lymphocyte ratio (NLR) is a promising predictive and prognostic factor in breast cancer. Studies have suggested that a higher NLR indicates poor prognosis. The current study is being done to evaluate the role of NLR in predicting the prognosis of a breast cancer patient being given standard of care. It is a retrospective observational study to find a correlation between high NLR and poor prognosis or disease progression.

Keywords: Breast Cancer, Biomarker, Neutrophil, Lymphocytes, Prognosis, Ratio

Introduction

Breast cancer is one of the most common types of cancer in women and accounts for nearly 25% of all cancer type worldwide and it is increasing at an alarming speed. It is the most common cancer in women in India and accounts for 14% of all cancers in women. It is the one of the most prevalent cancers in females in India right now with one in every 10 new cancers diagnosed in India annually being breast cancer, as per latest National Cancer Registry report, 2024.

It is very important to increase awareness regarding breast cancer in females so that they develop health seeking behaviour and go for diagnostic screening to detect it early because in case of early detection, breast cancer has a very good prognosis. Awareness can also lead to prevention by adopting healthy lifestyle measures like the right dietary habit and exercise. Besides there is need for more specific and sensitive biomarker for both diagnosis and prognosis.

Despite early diagnoses and therapeutic advances having considerably reduced mortality, breast cancer continues to be a threat. One major challenge in cancer management is attributed to treatment resistance in some cases.

In oncology, prognostic markers are clinical measures that are used to estimate an individual patient's risk of a future outcome, such as recurrence of disease after primary treatment. They thus facilitate individual treatment choice and aid in patient counselling.

There is always a need for specific and sensitive biomarker for seeing the girth, severity and prevalence of disease as well as its prognosis. In this regard, Neutrophil to lymphocyte ratio (NLR) values have been shown to mirror the tumor-induced inflammatory status and have been demonstrated to be a reliable prognostic tool across stages of disease and therapeutic approaches. The NLR may allow to further stratify patients with different likelihoods of deriving a significant clinical benefit. However, despite its accessibility, low cost, and easy interpretation, the NLR is still poorly used as a prognostic tool in daily clinical practice.

Studies have suggested that a higher NLR indicates poor prognosis. The current study is being done to evaluate the role of NLR in predicting the prognosis of a breast cancer patient being treated. It is a retrospective observational study to find a correlation between high NLR and poor prognosis or disease progression.

The NLR is of particular importance to cancer patients. In the year 1967, the importance of this ratio came into picture for the first time as a marker to measure exposure to toxic ozone gas, but its relevance to oncology came much later in the year 2014 when a study published in the Journal of the National Cancer Institute (JNCI) surveyed 100 journal articles that included a total of 40,559 cancer patients. The study demonstrated that an NLR greater than 4 was associated with an 81% increase in death. This was observed in all types of cancer at all sites, and all stages. The hazard ratio for disease-free survival was a whopping 227%. Thus, this ratio has been explored for its potential to predict the outcome of a number of cancers including breast cancer.

The importance of this ratio lies in the fact that the Neutrophil to Lymphocyte ratio (NLR) captures the intricate balance between pro-tumor neutrophilia and anti-tumor lymphocyte immunity.

Aim & Objectives

The main objective of the study is to verify the possible prognostic value of NLR in reference to breast cancer development and progression. The study also aims to correlate the various clinicopathological parameters with the prognosis of breast cancer.

Methodology

This is a retrospective observational study to evaluate the role of NLR in prognosis of breast cancer patients. IEC Approval was taken for the study to collect data from patient's file (IEC Approval No: 1030a/JNCH/RES/20/12/2024).

In the study herein presented, we retrospectively investigated the prognostic impact of NLR in around 50 patients with breast cancer who received Non-Adjuvant Chemotherapy (NACT) as primary treatment. The future scope of this study is to collect data from at least 500 patients. The current presentation is showcasing the data of 50 patients collected so far.

We collected the data from Medical Record Department and collected and compiled all relevant reports of the screened breast cancer patients including their socio-demographic details and their clinical characteristics including receptor status, histopathology report, and treatment pattern and all investigative reports including CBP.

The NLR was calculated from their blood profiles at the time of diagnosis before treatment, during the course of their treatment and till their last visit and they were assessed.

Result

The study demonstrates that the progression of breast cancer significantly increased with increasing levels of the neutrophil to lymphocyte ratio (NLR), calculated simply by dividing the number of neutrophils by number of lymphocytes.

The demographic and other clinic-pathological factors such as age, disease stage, tumor grade, nodal involvement, receptor status, subtype of the enrolled breast cancer patients have been shown below in **Table No. 1**. The study demonstrated that a higher NLR invariably resulted in disease progression leading to metastases and on the other hand, low NLR was indicative of improvement in patient condition as shown in **Table No. 2.**

Table 1. Demographic data and clinicopathologic characteristics of patients

Variables	Cases	Descriptive statistics (%)
Menopause		
Yes	27	54%
No	23	46%
Tumor size (cm)		
> 2	29	58%
≤ 2	21	42%
Type of Breast Cancer		
IDC	39	78%
ILC	6	12%
Mucinous	2	4%
Metastatic	3	6%
Lymph node metastases		
Positive	19	38%
Negative	31	62%
NLR at the end of data collection		
High	40	80%
Low	10	20%
Receptor status		
HR+, Her2+	1	2%
HR-, Her2-	2	4%
HR-, Her2+	13	26%
HR+,Her2-	34	68%
Histological grade		
G3	21	42%
G1/2	29	58%
Clinical Stages		
III–IV	29	58%
I–II	21	42%

Table No. 2: Showing correlation between NLR and Breast Cancer prognosis

NLR Status at the end of Data Collection	No. of Breast Cancer Patients	Status of Breast Cancer
< 1.00	10	Improved
2–3	12	Disease progression
> 3	28	Disease progression (Metastatic)

Discussion

The patients with breast cancer and an NLR above the defined cut-off (1.5-2.0) have consistently been found to have worse outcomes than patients with a lower NLR as per the current study. Consequently, NLR is also associated with treatment outcomes, tumor size, lymph nodes involvement, metastasis and clinical staging as these factors are indicators of disease progression.

The link between a high NLR and a high stage of the disease could be explained by lymphocytes' ability to slow the progression of cancer. Tumor-infiltrating lymphocytes have

been proven to improve cancer patient survival rates (Ohashi, R. *et al.,* 2006). Also, neutrophils on the other hand have been found to have role in tumor progression (Swierczak *et al.,* 2015). If we look at the individual role of Neutrophils and Lymphocytes in cancer development, we will understand in more detail their mechanism of action. Studies have shown that neutrophils support tumor growth by a number of mechanisms that helps in tumor initiation, growth as well as spread. The mechanism by which neutrophils support cancer initiation is by way of releasing reactive oxygen species (ROS) or proteases, they help in tumor growth by helping with angiogenesis and they play important role in spreading of cancer by escorting the circulating tumor cells for metastasis (Long *et al.,* 2021; Antonio et al., 2015). Therefore, there rise is indicative of cancer progression.

On the other hand, lymphocytes are the most crucial immune cells that fight all kind of unwanted invasion in body including cancer. Tumor-infiltrating lymphocytes (TILs) present in cancer microenvironment are an indication of an ongoing immune response against the cancer. Increase in some TILs like CD8+ T cells have been associated with a better prognosis in various cancers and therefore, their rise is indicative of a good defence against cancer development and their decline is indicative of poor prognosis.

Some other studies have also been done to understand in more detail the mechanism of action of neutrophils and cancer development. One such study done by Hurt *et al.,* (2017) provided evidence that tumor cells induce epigenetic changes in local neutrophils to promote tumor progression.

NLR appears to be independently prognostic after adjustment for disease stage, sites of metastatic disease, and established tumor markers (Feng Z *et al.,* 2016).

NLR may be used for stratification of cancer, correlates with the tumor size, stage of tumors, metastatic potential and lymphatic invasion. NLR has independent prognostic role regarding overall cancer free and cancer-specific survival. It is useful for monitoring oncological therapy, including biological and immune check point inhibitors treatment.

NLR is cheap, simple, fast responding and easily available parameter of stress and inflammation with high sensitivity and low specificity; it should be used routinely in medical setup including oncology for disease monitoring and treatment response. This can help in better clinical decision-making. Combined with other established biomarkers monitoring NLR can provide valuable information about a patient's cancer status. However, it's very important to interpret NLR values in the context of other available clinical information and consider its limitations.

Conclusion

We suggest that a high NLR may be an indicator of inadequate anti-cancer immune response and, therefore, of dismal long-term prognosis in patients with breast cancer treated with standard of care. This study provides preliminary evidence for NLR to predict the treatment

response and prognosis of patients with breast cancer.

It can be concluded from the study that NLR can proved to be a cost effective and non-invasive prognostic marker that can be utilized by medical fraternity for better management of breast cancer patients and it may find application in monitoring patients with other cancer types as well.

NLR is fast emerging as a personalized prognostic marker in breast cancer. Instead of determining a generalized cut-off value, individual baseline NLR and its dynamics with disease progression will help manage patients better. NLR is cheap, simple, fast responding and easily available parameter of stress and inflammation with high sensitivity and low specificity; it should be used routinely in emergency departments, ICUs, in acute medicine including oncology surgery, orthopedics, traumatology, cardiology, neurology, and psychiatry. NLR is used as a reliable and cheap marker of ongoing cancer-related inflammation and a valid indicator of prognosis of solid tumors. Besides its utility as a prognostic marker, it can also be utilized to help identify individuals who are at a higher risk of developing breast cancer leading to earlier intervention and preventative measures.

The future scope of the study includes long-term studies that need to be done on a larger population to get more clarity on this potential tumor prognostic marker.

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