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Research Article

The Value of Inflammatory Prognostic Index in Older Patients with Hormone Receptor Positive Metastatic Breast Cancer

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Abstract

Objectives: To search the prognostic value of an inflammation based prognostic score in older patients with hormone positive, Her2 negative metastatic breast cancer.

Methods: A retrospective study of 82 female patients aged 65 years and older with hormon receptor positive, Her-2 negative metastatic breast cancer diagnosed between 2011 and 2018 was conducted with collection of clinical and laboratory data. The inflammatory prognostic index (IPI) was calculated as C-reactive protein × NLR (neutrophil/ lymphocyte ratio)/serum albumin. Survival estimates were calculated with Kaplan-Meier method.

Results: The optimal cut-off points of IPI for the stratification of OS was found to be 0,75. Based on this cutoff value, patients were categorized as IPI-high and IPI-low group. High IPI was significantly associated with advanced stage at diagnosis. (p=0.03) The mean OS was 64 months in the IPI-high group and 66.9 months in the IPI-low group. (p=0,813) In patients receiving hormonotherapy in first line treatment PFS was 34.6 months in the IPI-low group and 14.5 months in the IPI high group, and a statistically significant difference was found compared to patients who received chemotherapy in the first line. (p=0,042).

Conclusion: Measurement of systemic inflammatory response in older adults with metastatic breast cancer is reliable, available, and can be clinically incorporated into current geriatric oncology algorithms.

Keywords: Breast cancer, index, inflammatory, metastatic, older, prognosis

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The incidence of breast cancer increases with age.[1] The majority (58%) of breast cancer deaths occur in women 65 years of age or older.[2] By 2030, it is estimated that the proportion of older adults will double from 14% to 20% of the total U.S. population.[3] However in most prospective clinical studies, the older population was not included.[4] Therefore, information about breast cancer in the older adults has not yet been conclusive, and the management of these cases is based on extrapolation of data in young patients.

In the geriatric patient group, physicians have difficulties in making the right treatment decision.[5] Therefore, there is a need for easy-to-use and time-saving tools that can predict survival.

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As a sign of cancer development and progression, inflammation facilitates cancer cell survival.[6] The prognostic value of inflammation markers has been demonstrated in various cancers.[7] In this respect, it has come to the fore to evaluate the use of inflammatory prognostic index (IPI) calculated by C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR) and albumin, which have not previously been studied in breast cancer.[8]

In the general population of older adults, inflammatory markers are predictors of adverse health outcomes. We planned to evaluate the relationship between IPI, a marker that can be easily calculated in clinical practice, and survival in older patients with metastatic breast cancer.

Methods

Medical records of 82 female, older than 65 years of age, hormone receptor positive, human epidermal growth factor receptor 2 (HER2) negative metastatic breast cancer patients who were followed up at Oncology Clinics of two university hospitals between May 2011 and November 2018 were reviewed retrospectively. Ethics committee approval dated 2I/04/2020 and numbered I5227 was obtained. Patient demographics, Eastern Cooperative Oncology Group (ECOG) performance score, tumor characteristics, diagnostic stage, treatment modalities, neutrophil, lymphocyte, albumin, and CRP levels at the time of metastasis were recorded. NLR was calculated by dividing absolute neutrophil count by absolute lymphocyte count. IPI was calculated by the following formula: CRP × NLR / serum albumin. The association between inflammatory markers and overall survival (OS) and progression-free survival (PFS) was evaluated. OS was calculated from the diagnosis of the patient to the date of death from any cause. PFS was calculated using the time interval between the onset of treatment and the date of the first visit in which progression was detected.

Statistical Analysis

Categorical variables were compared using Chi-square or Fisher's exact test with odds ratio (OR) and corresponding 95 % confidence interval (CI). Receiver Operating Characteristic (ROC) curve analysis was used to determine the cut-off value for NLR and IPI (respectively; 2.22 and 0.75). Statistical analyses were performed using SPSS 22.0 software (SPSS Inc. Chicago, IL). All statistical assessments were two-sided and a p-value of 0.05 was considered statistically significant.

Results

Table 1 presents the patient characteristics of 82 older women with hormon receptor positive, Her-2 negative metastatic breast cancer. The median age was 69 years (range 65 to 91). The most common subtype of breast cancer was invasive ductal carcinoma (72%) and 31.7% patients had stage 4 disease at the time of diagnosis.

Table 1. Clinical characteristics of the study population

Clinical characteristics of the patients	% (n)
ECOG performance score	
0	30.5 (25)
1	56.1 (46)
2	13.4 (11)
Disease Stage	
I	8.5 (7)
II	35.4 (29)
III	24.4 (20)
IV	31.7 (26)
Tumor Localisation	
Right	40.2 (33)
Left	58.5 (48)
Bilateral	1.2 (1)
Hormone Receptor	
ER +	96.3 (79)
PR +	79.3 (65)
Tumor Grade	
1	4.9 (4)
2	59.8 (49)
3	18.3 (15)
Not known	17.1 (14)
Tumor Histology	
IDC	72 (59)
ILC	11 (9)
Mixed	13.4 (11)
Other	3.7 (3)
Breast Surgery	
Lumpectomy	58.5 (48)
Mastectomy	25.6 (21)
No	15.9 (13)
Systemic treatment	
AdHT	63 (52)
NACT	8.5 (7)
AdCT	50 (41)
First line treatment for Stage 4 disease	
HT	41.5 (34)
CT	35.4 (29)
Unknown	23.1 (19)

ECOG: Eastern Cooperative Oncology Group; ER: Estrogen receptor; PR: Progesteron receptor; IDC: Infiltrating ductal carcinoma; ILC: Invasive lobular carcinoma; AdHT: Adjuvant Hormonotherapy; NACT: Neoadjuvant Chemotherapy; AdCT: Adjuvant Chemotherapy.

NLR and IPI rates were calculated separately for all patients. It was found that as NLR increased, IPI increased and there was a correlation between NLR and IPI. However survival analyses did not reach statistically significant values with

NLR. In patients with stage 4 breast cancer, OS was 68.1 months in patients with high NLR and 60.6 months in patients with low NLR (p=0.589).

Using the ROC curve analysis, the optimal cut-off points of IPI for the stratification of OS was found to be 0,75 (Fig. 2). Based on this cutoff value, 37 (45.1%) patients were categorized as IPI-high group while the remaining 45 (54.9%) patients as IPI-low group. High IPI was significantly associated with advanced stage at diagnosis. (Stage III-IV; p=0.03) Age, ECOG, T stage, lymph node involvement and ki-67 were similar between two groups. A positive correlation was found between the increase in IPI score and the N stage, and this correlation was statistically significant (p=0.031).

The mean OS was 64 months in the IPI-high group and 66.9 months in the IPI-low group. Although OS difference was separated numerically, it did not reach statistical significance (p=0.813). Considering the relationship between the first-line treatment for metastatic disease and the inflammatory index, in the IPI-low group the mean PFS with chemotherapy was 5.6 months while PFS with hormonotherapy was 34.6 months, p values were 0.656 and 0.042 respectively. PFS analysis was performed only for the patients whose treatment onset and end date data were clearly available. (Table 2) As shown in Figure 1 the difference in PFS compared to the IPI groups was statistically significant in patients who received hormonotherapy as first-line therapy for metastatic disease (p=0.042) (Fig. 1).

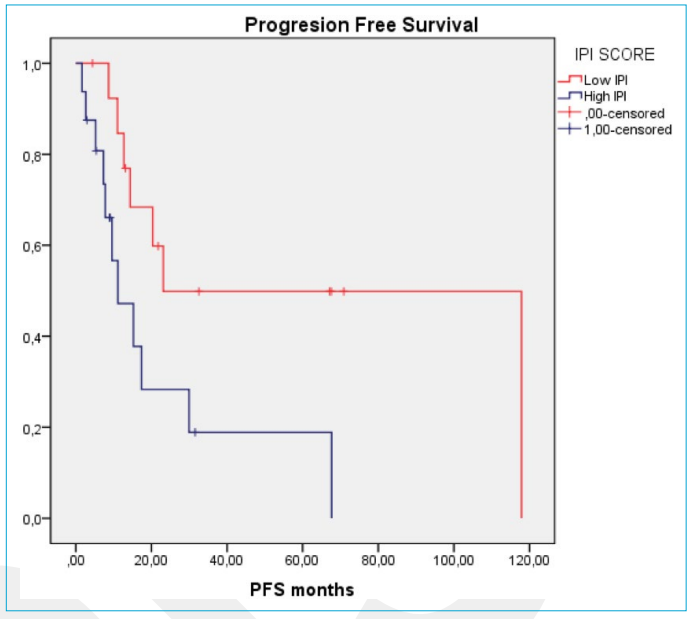

Figure 1. Comparison of First Line Hormonotherapy Responses Between IPI Groups.

Discussion

Elderly patients represent the fastest growing segment of the oncology population. It is predicted that by 2030, approximately 70% of cancers in the United States will be diagnosed in people over 65 years old.[9] Although the number of elderly patients with breast cancer is increasing, there is limited information about the biology and clinical outcomes of breast cancer by age. Older age has been associated with a decrease in tumor proliferative factors, and older patients often present with well-differentiated tumors and positive hormone receptor status that constitutes our study population.[10] The relatively less inclusion of patients aged 65 and over in clinical trials is an important factor contributing to the limited knowledge on cancer management. Despite the scarcity of data on this population, oncologists consider age as an important determi-

Table 2. Progression-free survival according to first line therapy options

	IPI	N (%)	Mean (months)	SD	p
PFS with CT	Low	6 (23.1)	5.6	1.3	0.656
	High	20 (76.9)	6.4	1.1	
PFS with HT	Low	14 (46.7)	34.6	8.8	0.042
	High	16 (53.3)	14.5	4.1	
PFS regardless of treatment	Low	20 (35.7)	28.7	7.1	0.006
	High	36 (64.3)	8.6	1.2	

PFS: Progression-free survival; IPI: Inflammatory prognostic index; CT: Chemotherapy; HT: Hormonotherapy; SD: Standart deviation. N: Number of patients.

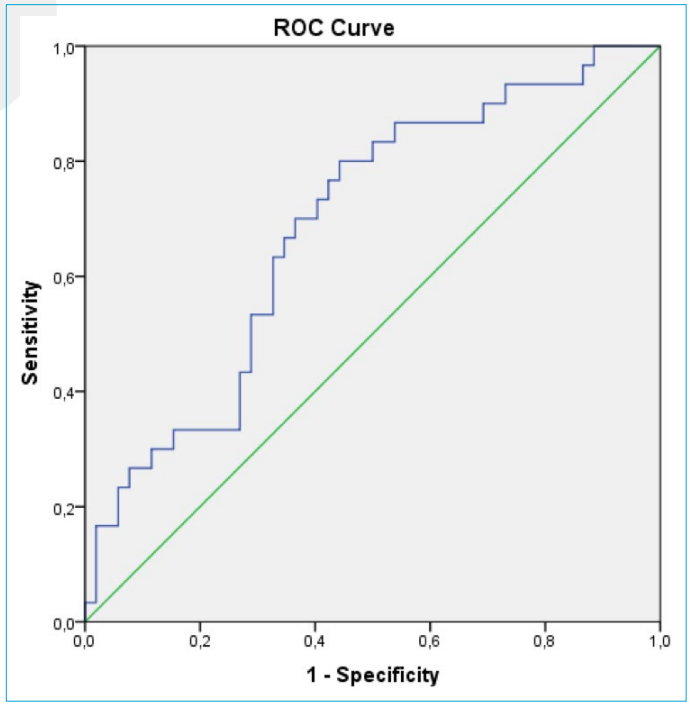

Figure 2. ROC curve of IPI.

nant of treatment and breast cancer treatment approaches differ depending on age.[11] However, considering the heterogeneity of individuals in advanced age groups, age is not an appropriate criterion for breast treatment decisions. On the other hand, in advanced cancer, the inflammatory response of the host is thought to be an important predictor of survival independent of tumor stage.[12] Recent studies have shown that survival estimation can be made using inflammatory markers in elderly cancer patients, and thus treatment can be selected using markers other than age. In the study of Nishijima et al., it was reported that NLR was associated with OS independent of previously reported prognostic geriatric evaluations, and it was an important indicator of worse survival.[13]

A systematic review of CRP found higher concentrations in cancer patients than subjects with benign diseases or healthy controls in most cross-sectional and case-control studies reviewed.[14] In another study, significant associations between reduced overall survival and reduced disease-free survival and high CRP concentrations were observed, and this association was independent of disease stage, self-reported cardiovascular events, estradiol concentrations, smoking, and physical activity.[15] Similarly, in a study conducted on 85 metastatic breast cancer patients, high pre-treatment CRP was associated with a decrease in survival.[16] In the study of Lis CG et al., it was found that low serum albumin levels negatively affect survival at a statistically significant level for all stages of breast cancer.[17] The Glasgow prognostic score (GPS) based on CRP and albumin, which are markers of inflammation in the blood, has also been validated in more than 60 studies on patients with cancer and predicts survival. Given that albumin concentrations reflect both systemic inflammation and the amount of lean tissue, it has been interesting to examine the prognostic value of the combination of high C-reactive protein level and hypoalbuminemia.[18] In accordance with all the aforementioned literature data, in our study which evaluated the IPI score calculated with the combination of CRP, albumin and NLR in women over 65 years of age with metastatic breast cancer, a positive correlation between NLR and IPI was confirmed.

High IPI was significantly associated with advanced stage at diagnosis. This finding suggests that besides the increase in cancer risk with aging, the severity of inflammatory response in the older population may be related to the cancer stage at the time of diagnosis.

Although there was no significant correlation between the T stage and IPI scores of the patients, it was observed that there was a positive correlation with the N stage (p=0.031).

Despite the fact that the survival contribution of axillary surgery is not clear in older patients and the rate of axillary surgery decreases with increasing age,[19] in the light of our finding, it is necessary to determine the N stage meticulously because it predicts prognosis in the geriatric population when evaluated together with IPI.

While some elderly patients are willing to undergo treatment burden to improve their survival, the vast majority refuse treatments that result in severe functional (74%) or cognitive (89%) impairments.[20] In terms of breast cancer, breast tumors diagnosed in older women are thought to be biologically quieter, and the prevalence of comorbid diseases is higher in this population. Therefore, the choice of treatment tends to be less aggressive for older women. The aim of treatment in patients with metastases is to control the progression of the cancer and to maintain the highest function and quality of life.

In addition to well-defined prognostic factors associated with the tumor, patient characteristics may also be associated with the survival of breast cancer, so IPI calculated with easily accessible parameters in clinical practice can guide the choice of treatment.[21]

In our study, PFS was found to be 34.6 months in patients with low IPI scores and was 14.5 months in the high IPI group when hormonotherapy was used in the first line treatment, and a statistically significant difference was found compared to patients who received chemotherapy in the first line treatment (p=0.042). With this finding, it can be predicted that the prognosis is better in older patients with low inflammation score and if there is no indication for chemotherapy such as visceral crisis, it would be appropriate to choose hormonotherapy. Since the treatment is palliative in metastatic disease, avoiding toxicity seems to be a priority in the treatments to be chosen, and endocrine treatment is the first choice if there are no life-threatening metastases in hormone-positive patients. Besides there is also a group of patients who avoid treatment at the metastatic stage due to the fact that death from causes other than cancer is more likely for many elderly patients.[22] The results obtained in our study suggest that the IPI score, which can be easily calculated in daily practice, will help determine the group that will benefit more from endocrine treatment.

Additionally, in our study population, no significant results were obtained in the survival analysis performed with the cut off value determined for NLR. Nevertheless, achieving results that determine the choice of treatment with IPI supports the idea that IPI score may be a more reliable marker than NLR.

However, our study had several limitations. The major limitation is its retrospective nature.

Second, medical records did not include geriatric assessment so that the frailty scores, nutritional status and cognitive performance of the patients were missing. Lastly, these results may not be generalizable, as they are derived from only two academic tertiary-care center. Regardless of these limitations, our findings are clinically meaningful. Multicenter prospective studies, which clearly perform comprehensive geriatric assesments, would be helpful in addressing these limitations.

As a result, this study evaluated the prognostic value of the IPI score obtained with the combination of cellular inflammation markers in older adults with cancer. For older patients, the IPI score can be used in conjunction with other geriatric assessment scales to customize therapy based on individual patient characteristics. Still larger studies are needed to support this view and compare IPI's performance to current tools in geriatric oncology.

Conclusion

Although there are well-established prognostic factors to predict survival at the time of diagnosis in cancer patients, it is more problematic to predict survival in metastatic disease.

This study suggests that IPI may be useful for evaluating survival in older patients with metastatic hormone-positive, Her-2 negative breast cancer and for determining the choice of first-line treatment. Systemic inflammation based prognostic scores both identify high-risk patients and provide appropriate targets for new clinical trials.

Disclosures

Ethics Committee Approval: Approval dated 2l /04 /2020 and numbered l5227 was obtained.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.P.E., A.D.; Design – A.P.E., A.D., F.E.; Supervision – A.D., E.O.; Materials – A.D., E.O.; Data collection &/or processing – S.Y., M.S., B.D., A.O.; Analysis and/or interpretation – A.P.E., F.E., A.O.; Literature search – A.P.E., F.E.S.Y., M.S.,B.D.; Writing – A.P.E., F.E., A.O.; Critical review – A.D.

References

1. Yancik R, Ries LG, Yates JW. Breast cancer in aging women. A population-based study of contrasts in stage, surgery, and survival. Cancer 1989;63:976–81.
2. Cancer Facts and Figures 2008. American Cancer Society, Surveillance Research. American Cancer Society, Atlanta, GA; 2008. Available from: https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2008.html
3. Jolly TA, Williams GR, Bushan S, Pergolotti M, Nyrop KA, Jones EL, et al. Adjuvant treatment for older women with invasive breast cancer. Womens Health (Lond) 2016;12:129–45.
4. Kemeny MM, Peterson BL, Kornblith AB, Muss HB, Wheeler J, Levine E, et al. Barriers to clinical trial participation by older women with breast cancer. J Clin Oncol 2003;21:2268–75.
5. Yancik R, Wesley MN, Ries LA, Havlik RJ, Edwards BK, Yates JW. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA 2001;285:885–92.
6. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell 2011;144:646–74.
7. Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Future Oncol 2010;6:149–63.
8. Dirican N, Dirican A, Anar C, Atalay S, Ozturk O, Bircan A, et al. New inflammatory prognostic index, based on c-reactive protein, the neutrophil to lymphocyte ratio and serum albumin is useful for predicting prognosis in non-small cell lung cancer Cases. Asian Pac J Cancer Prev 2016;17:5101–6.
9. Smith BD, Smith GL, Hurria A, Hortobagyi GN, Buchholz TA. Future of cancer incidence in the United States: Burdens upon an aging, changing nation. J Clin Oncol 2009;27:2758–65.
10. van de Water W, Markopoulos C, van de Velde CJ, Seynaeve C, Hasenburg A, Rea D, et al. Association between age at diagnosis and disease-specific mortality among postmenopausal women with hormone receptor-positive breast cancer. JAMA 2012;307:590–7.
11. Diab SG, Elledge RM, Clark GM. Tumor characteristics and clinical outcome of elderly women with breast cancer. J Natl Cancer Inst 2000;92;550–6.
12. MacDonald N. Cancer cachexia and targeting chronic inflammation: A unified approach to cancer treatment and palliative/supportive care. J Support Oncol 2007;5:157–62.
13. Nishijima TF, Deal AM, Lund JL, Nyrop KA, Muss HB, Sanoff HK. Inflammatory markers and overall survival in older adults with cancer. J Geriatr Oncol 2019;10:279–84.
14. Heikkilä K, Harris R, Lowe G, Rumley A, Yarnell J, Ben-Shlomo Y, et al. Associations of circulating C-reactive protein and interleukin-6 with cancer risk: Findings from two prospective cohorts and a meta-analysis. Cancer Causes Control 2009;20:15–26.
15. Pierce BL, Ballard-Barbash R, Bernstein L, Baumgartner KB, Neuhouser ML, Wener MH, et al. Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients. J Clin Oncol 2009;27:3437–44.
16. Albuquerque KV, Price MR, Badley RA, Jonrup I, Pearson D, Blamey RW, et al. Pre-treatment serum levels of tumour markers in metastatic breast cancer: A prospective assessment of their role in predicting response to therapy and survival. Eur J Surg Oncol 1995;21:504–9.
17. Lis CG, Grutsch JF, Vashi PG, Lammersfeld CA. Is serum albu-

min an independent predictor of survival in patients with breast cancer? JPEN J Parenter Enteral Nutr 2003;27:10–5.
18. McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: A decade of experience in patients with cancer. Cancer Treat Rev 2013;39:534–40.
19. Edge SB, Gold K, Berg CD, Meropol NJ, Tsangaris TN, Gray L, et al. Outcomes and preferences for treatment in older women nationwide study research team. Patient and provider characteristics that affect the use of axillary dissection in older women with stage I-II breast carcinoma. Cancer 2002;94:2534–41.
20. Fried TR, Bradley EH, Towle VR, Allore H. Understanding the treatment preferences of seriously ill patients. N Engl J Med 2002;346:1061–6.
21. Singh T, Newman AB. Inflammatory markers in population studies of aging. Ageing Res Rev 2011;10:319–29.
22. Bulut G, Oytun MG, Almuradova E, Dogu BB, Karaca B. Breast cancer in women aged 75 years and older. Eur J Geriatric Gerontol 2021;3:117–23.

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