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Original article

Correlation between carcinoembryonic antigen, cancer antigen 15-3, and neutrophil–lymphocyte ratio on metastasis and progression-free survival of breast cancer

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Abstract. *Background and aim:* Blood and tumor markers have been studied as predictive and prognostic factors in breast cancer (BC). To assess the relationships of the tumor markers cancer antigen 15-3 (CA 15-3) and carcinoembryonic antigen (CEA) and the neutrophil–lymphocyte ratio (NLR) with the incidence of metastasis and progression-free survival (PFS) in BC. *Methods:* This observational analytical study used a cohort design. The population was BC patients who had undergone mastectomy or breast-conserving treatment. Patients received CEA and CA 15-3 examinations and were assessed radiologically for metastases, with follow-up of up to 24 months. Differences in patient PFS levels depending on NLR, CEA, and CA 15-3 were assessed using Kaplan–Meier analysis. *Results:* One male and 159 female patients were included, with a mean age of 48.3 ± 9.18 years. The mean NLR, CEA, and CA 15-3 were 22.51 ± 94.1, 73.05 ± 212.99, and 2.56 ± 3.48, respectively. Based on a mean PFS of 12.16 ± 0.45, 38.4% of patients experienced metastases. A significant relationship with the incidence of metastasis existed for CA 15-3 and CEA levels but not NLR. Likewise, PFS did not show a significant relationship with NLR, CA 15-3, or CEA. Survival analysis showed no significant relationship. *Conclusions*: CEA and CA 15-3 can be negative prognostic factors for BC metastasis. These results can be compared with other studies, specifically answering the role of predictive and prognostic factors of NLR, CEA, and CA 15-3 in BC patients. (www.actabiomedica.it)

Key words: breast cancer, progression-free survival, cancer antigen 15-3, neutrophil–lymphocyte ratio, carcinoembryonic antigen

Introduction

Breast cancer (BC) was the main cause of cancer in women globally in 2020 (1), with an estimated 2.3 million new cases: 11.7% of all cancer cases. It is also the fifth leading cause of cancer mortality worldwide, with around 685,000 deaths annually (2–4). Data from Baseline Health Research in 2013 and 2018 show an increase in the prevalence of cancer in Indonesia, from 1.4% to 1.49% (1). This could be because female-dominant types of cancer, such as BC and cervical cancer, are the types most commonly reported in Indonesia. This type of cancer also has better early-detection coverage than other types (1).

The neutrophil–lymphocyte ratio (NLR) in particular has become a predictive and prognostic indicator

for inflammatory blood markers in recent years. It describes the proportion derived from the total number of neutrophils and total number of lymphocytes. Before chemotherapy begins, lymphopenia and elevated NLR are occasionally related to a worse prognosis for various types of cancer, including BC, and a worse response to neoadjuvant chemotherapy (5).

A tumor marker is a molecule or substance that can be measured in serum, plasma, or other body fluids, tissue extracts, or paraffin tissue preparations and appears both qualitatively and quantitatively in precancerous and cancerous conditions (6). Well-known tumor markers for BC are carcino-embryonic antigen (CEA) and mucin-like glycoprotein (CA15-3) (7,8). The CA 15-3 examination is to detect MUC1, which is one of the mucin groups. Increasing evidence suggests that increased tumor markers are associated with BC progression. Increased serum levels of tumor markers can be found on average 2–18 months before metastatic BC is clinically detected (9).

This study aimed to determine the relationship of tumor marker levels, specifically CA 15-3 and CEA, and NLR with the incidence of metastasis and progression-free survival (PSF) in patients with BC.

Materials and methods

This was an observational analytical study with a cohort design. The participants were all patients diagnosed with BC at Dr. Wahidin Sudirohusodo Hospital Makassar, Indonesia, from January to December 2020. The inclusion criteria were: 1) BC patients aged 18 to ≤70 years; 2) having undergone mastectomy or breast-conserving treatment; 3) complete data on serum levels of CEA and CA 15-3; 4) radiological examination (chest photo, ultrasound, CT scan, or MRI) proving metastatic BC, if present; 5) having received an explanation of the research and agreed to be involved. The exclusion criteria were: 1) patients who had not undergone surgery (mastectomy or BCT); 2) incomplete patient data on serum levels of CEA and CA 15-3; 3) patients with other types of cancer (e.g., ovarian, colorectal, liver, or lung cancer); 4) patients who could not be contacted for follow-up. Medical record data taken as research data included age when BC was diagnosed, gender, stage based on TNM rules, NLR, CA 15-3 and CEA values, radiological examination results, and progression-free survival (PFS) (followed up for 24 months).

CA 15-3

CA 15-3 is a high-molecular-weight glycoprotein released from the surface of epithelial cells (10). CA 15-3 levels in blood serum samples were measured using the enzyme-linked fluorescent assay (ELFA) method on the Roche Elecsys 2010 device (Roche Diagnostics Corp., Indianapolis, USA) and expressed in U/mL, where cut-off values for CA 15–3 is 25.0 U/mL. The classification of CA 15-3 levels was normal or high.

CEA

CEA is a non-mucin glycoprotein secreted by digestive tract epithelial cells in normal fetuses and by tumors in adults (11). CEA levels in blood serum samples were measured using the ELFA method on the Roche Elecsys 2010 device (Roche Diagnostics Corp., Indianapolis, USA) and expressed in ng/mL, where cut-off value is 4.70 ng/mL. The classification of CEA levels was normal or high.

NLR

The NLR is a straightforward ratio determined by counting the neutrophils and lymphocytes in peripheral blood (12). The classification of NLR levels was low, normal, or high.

PFS

PFS is defined as the time between treatment and tumor progression or death from any cause, as a surrogate endpoint of overall survival (OS) (13,14). In this study, follow-up was carried out for up to 24 months and graded as ≤12 months or >12 months. PFS was assessed based on this grading in patients with advanced BC stages or evidence of metastasis based on radiological examination.

Breast cancer metastases

Patient data was obtained based on anamnesis, physical examination, and radiological findings. An abdominal ultrasound examination showing a hypoechoic or hyperechoic halo appearance or an abdominal CT scan showing metastatic nodules in the liver was taken as a sign of liver metastases. A chest X-ray examination showing a calcified or bubbling (cavitate) nodule or pleural effusion was taken as a sign of lung metastasis. A thoraco-lumbosacral X-ray or MRI of the vertebrae showing compression fractures or metastatic lytic lesions (lytic metastases), whitish spots (blastic metastases), or both (mixed metastases) in the vertebrae or other extremity bones, or other pathological fractures, were taken as signs of bone metastasis. A CT scan of the head showing a hyperdense, nodular, or ring-like image can be obtained if the tumor has lost its blood supply as a sign of brain metastasis. An MRI of the brain with a sugar-coating image was a sign of spinal fluid metastasis. The classification of metastases was based on their presence or absence.

Statistical analysis

The data were analyzed statistically using SPSS version 22 (IBM Corp., Armonk, NY, USA). Univariate data analysis was performed to determine the distribution of patient characteristic data. Statistical analysis for bivariate analysis used the Spearman test method for categorical data and the Pearson test for numerical data. The log-rank approach (Mantel–Cox) in Kaplan–Meier analysis was used to ascertain variations in patient PFS according to NLR, CEA, and CA 15-3 levels.

Table 1. Participant characteristics.

Variable	n	%
Sex		
Female	158	99.4
Male	1	0.6
Age (years)		
20–30	4	2.4
31–40	24	15.1
41–50	68	42.8
51–60	47	29.6
>60	16	10.1
Metastatic		
No	98	61.6
Bone	18	11.3
Brain	8	5.0
Lung	19	11.9
Bone and liver	5	3.1
Bone and lung	6	3.8
Lung and liver	1	0.6
Bone. lung, and liver	2	1.3
Bone, liver, and brain	1	0.6
Bone, lung, and brain	1	0.6

Table 2. Descriptive sample.

Variable	Mean	SD
Age (years)	48.3	9.18
CEA (U/mL)	22.51	94.1
CA 15-3 (ng/mL)	73.05	212.99
NLR	2.56	3.48
PFS	25.85	4.628

Results

A total of 507 patients were selected, and 348 were excluded because medical records were not found or examinations were incomplete. Therefore, 159 patients met the study criteria (Table 1).

The mean age of the patients was 48.3 ± 9.18 years. Most were female, with only one male patient. The average CEA level was 22.51 ± 94.1. The average CA 15-3 level was 73.05 ± 212.99. The average NLR value was 2.56 ± 3.48 (Table 2). Most patients (98) were without metastases, with lung metastases in 19 patients and bone metastases in 18. The lowest PFS was 2 months, and the highest was 18 months, with an average of 12.16 ± 0.45.

No significant relationship existed between NLR levels and the incidence of metastasis ($p = 0.532$). A significant relationship was found between CEA levels and the incidence of metastasis ($p = 0.001$). A significant

Table 3. Correlation of NLR, CEA, and CA15-3 with metastasis.

Variable	Metastasis		p-value
	Yes	No	
NLR			
Low	3	3	0.532*
Normal	47	81	
High	11	14	
CEA			
Normal	32	29	0.001*
High	81	17	
CA 15-3			
Normal	34	77	0.003*
High	27	21	

Table 4. Correlation of NLR, CEA, and CA15-3 with PFS.

Variable	PFS		p-value
	≤ 12 months	> 12 months	
NLR			
Low	0	3	0.848**
Normal	22	25	
High	6	5	
CEA			
Normal	18	14	0.526**
High	10	19	
CA 15-3			
Normal	16	12	0.079**
High	18	15	

relationship existed between CA15-3 levels and the incidence of metastasis (p = 0.003; Table 3).

Concerning PFS, no significant relationship was found between NLR and the incidence of metastasis (p = 0.848). Similarly, we found no significant relationship between CEA levels and the incidence of metastasis (p = 0.526). No significant relationship between CA15-3 levels and the incidence of metastasis existed (p = 0.079; Table 4).

Figure 1 and Table 5 show the Kaplan–Meier analysis of the log-rank (Mantel–Cox) method based on survival analysis and the log-rank test (Mantel–Cox) of PFS on NLR, CEA, and CA15-3. It showed no significant differences between any variables (p > 0.05).

Discussion

This study found no significant relationship between the NLR and the incidence of metastasis in BC. However, Orditura et al. (15) examined NLR as a predictor of distant-metastasis-free survival (DMFS). From the entire population of 300 patients, 134 had a low NLR, and 166 had a high NLR, with an NLR limit value of 1.97. DMFS rates at 1, 3, 6, 9, 12, and 15 years were better in low-NLR patients than in high-NLR patients, which was statistically significant. In addition, Inoue et al. (16) assessed the clinical significance of NLR in oligometastatic BC. The low-NLR group included patients significantly older at the primary cancer compared to the high-NLR group. A lower NLR indicated better OS.

This study found no significant relationship between the NLR value and PFS in BC patients. This is in line with Rubio et al. (17), who examined NLR as an independent predictor of survival from metastatic BC. NLR values were higher than the median value cut-off point (>2.32) of the patient outcome when metastatic BC was categorized based on the visceral crisis with no significant difference for PFS (p = 0.43) but statistically significantly associated with OS (p = 0.048). Additionally, it was not significant with other clinical covariates (age at diagnosis, performance status, visceral disease, and central nervous system involvement). NLR was not an independent predictor of PFS in the multivariate analysis, which included all factors that were significant in the univariate study (17).

Caiyu Lou et al. (18) examined the relationships of blood levels of PLR, NLR, and HALP with the effectiveness of neoadjuvant chemotherapy and the prognosis for triple-negative BC. The survival rate of the group with high NLR values was statistically lower than that of the group with low NLR values (χ^2 = 15.441, p < 0.001).

In BC, CEA is the most significant tumor marker (19–21). Of patients with initial BC, 13% had elevated serum CEA levels. An association existed of tumor markers with nodal involvement and tumor size.

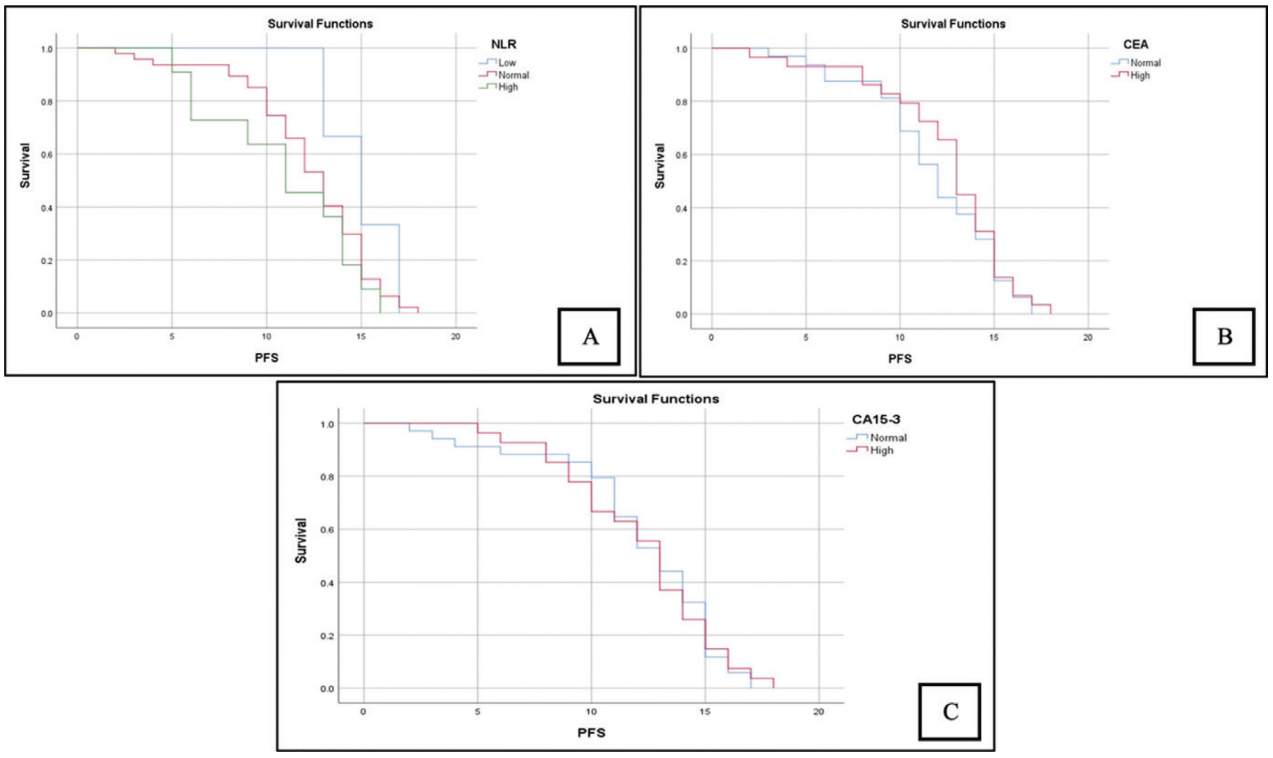

Figure 1. Progression-free survival (PFS) based on NLR (A), based on CEA (B), and based on CA 15-3 (C), using Kaplan–Meier analysis.

Table 5. Survival analysis of PFS on NLR, CEA, and CA15-3

Variable	Mean ± SD	Log-rank (Mantel–Cox)
NLR	12.16 ± 0.453	0.241
CEA		0.427
CA15-3		0.971

Patients with nodal involvement and those with larger tumors had considerably higher concentrations. CEA has a low sensitivity in primary diagnosis, so it is not recommended for screening but can be useful in determining prognosis, response to therapy, and follow-up monitoring (22). According to studies, with a waiting period of 2 to 18 months, CEA can identify 40–60% of recurrences before any radiological or clinical signs (22–24).

This study found no significant relationship of CEA levels with PFS or metastasis in BC patients. This differs from research conducted by Yang et al. (25), who observed that high CEA levels had a shorter PFS, with an average of 12.10 months, in contrast to a PFS duration of 18.33 months in individuals with normal levels. In terms of OS, another study examined the prognostic significance of elevated preoperative tumor markers (CEA and CA15-3) in patients with BC. Patients with higher-than-normal CEA and CA15-3 levels had lower OS, particularly those using Luminal (Luminal A and or Luminal B). Elevated CEA levels were the sole independent predictive factor for the HER2 subtype. Nevertheless, increased preoperative CEA and CA15-3 levels are not significant OS predictors for the triple-negative BC (TNBC) subtype (8,26).

One commonly evaluated tumor marker in BC is CA 15-3 (10,27,28). Elevated CA 15-3 serum levels were found in 19% of primary BC patients. Like CEA (19–21), CA 15-3 has a low sensitivity in primary diagnosis, so it is not recommended for screening but can be useful in determining prognosis, response to therapy, and follow-up monitoring (22).

Wang et al. (29) found that the sensitivity of CA15-3 in the diagnosis of metastatic BC was 44.5%.

The present study found no significant relationship between CA15-3 levels and PFS or metastasis in BC patients. This is consistent with a study by Yang et al. (25), who found that patients with elevated CA15-3 levels had a mean PFS of 12.50 months shorter than patients with normal CA15-3 levels (18.53 months).

Elevated tumor marker CA 15-3 and CEA levels can indicate BC progression and the presence of undetected metastatic foci (25,30,31). Therefore, these may be good markers of BC development regarding PFS (25).

This research has several limitations. The number of samples does not represent a population, which may have influenced the research results and loss to follow-up. More multi-center studies are needed on other clinicopathological parameters, such as lymphovascular infiltration, presence or absence of metastases, comorbid factors, and menopausal status, and their influence on BC prognostication.

Conclusion

High levels of CA 15-3 and CEA can be a negative predictor for the incidence of metastasis and survival of patients with BC. In this study, CEA and CA 15-3 could be used as markers for the incidence of metastases and PFS in patients with BC. NLR did not show a significant difference in the incidence of metastasis or PFS in patients with BC. The results of this study can be used in comparison with other studies, specifically answering the role of predictive and prognostic factors for NLR, CEA, and CA 15-3 in patients with BC.

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Authors Contribution: MAA (Concept, Design, Resources, Materials, Data Collection and Processing, Analysis and Interpretation, Literature Search, Writing Manuscript). SAS (Concept, Design, Supervision, Analysis and Interpretation, Literature Search), JP (Concept, Design, Supervision, Analysis and Interpretation, Literature Search), PRI (Concept, Design, Supervision, Analysis and Interpretation, Literature Search), FH (Concept, Design, Critical Review), RM (Concept, Design, Critical Review), MF (Concept, Design, Analysis and Interpretation, Critical Review).

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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