Prognostic value of the neutrophil-lymphocyte, platelet-lymphocyte and monocyte-lymphocyte ratio in breast cancer patients

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Abstract. The aim of the present study was to assess the blood the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and monocyte-lymphocyte ratio (MLR) as prognostic factors in breast cancer (BC) patients. A retrospective analysis of 436 BC patients who were treated at COI (Gliwice, Poland) between January 2005 and June 2018 was performed. The prognostic value [overall survival (OS)] of the pre-treatment PLR, NLR and MLR was assessed by univariate and multivariate analysis. The 5-year OS was lower in the NLR >2.65 compared with that in the NLR≤2.65 group (82.5 vs. 89.6%; P=0.053), and significantly lower in the subgroup of triple-negative breast cancer (TNBC; 70.3 vs. 89.3%; P=0.034) and in patients whose tumors had an estrogen receptor-negative [ER(-)] status (66.6 vs. 83.6%; P=0.018). The 5-year OS was lower in patients with PLR >190.9 compared with that in the PLR≤190.9 group (78.7 vs. 89.4%; P=0.020). A poor OS rate associated with an elevated PLR was also observed in the subgroups with TNBC (68.2 vs. 88.5%; P=0.032) and with ER(-) status tumors (57.7 vs. 83.6%; P=0.002). An elevated MLR (>0.28) was not associated with OS time (P=0.830). Multivariate analysis revealed that the NLR and PLR were insignificant negative prognostic factors, except for the subgroup of patients with ER(-) tumors, where an elevated NLR [hazard ratio (HR)=2.40; 95% confidence interval (CI): 1.20-4.80; P=0.013] and a higher PLR (HR=2.51; 95%CI: 1.23-5.14; P=0.012) were independent prognostic factors for poor OS together with lymph node metastasis ([HR=5.47; 95%CI: 2.46-12.15; P=0.0001 and HR=4.82; 95% CI: 2.15-10.78; P=0.0001), respectively. The present results revealed that an elevated NLR (>2.65) and PLR (>190.9) are associated with poor OS in BC patients. In the ER(-) subgroup of patients, an elevated NLR and PLR were significant independent prognostic factors. However, the MLR did not affect OS.

Introduction

Breast cancer (BC) is a common malignancy in women. In the Silesian region of Poland, the BC-associated morbidity was reported to be 21% of cancer cases in females in the year 2013. Cancer-associated mortality has been reported in 15% of BC patients. Traditional prognostic factors in BC patients are metastases in lymph/axillary nodes, tumor size, tumor grade (histologic or nuclear), vessel infiltration, the estrogen receptor (ER) and progesterone receptor (PR) status, and HER2 overexpression (1).

Inflammation impacts each step of tumorigenesis, including tumor initiation, promotion and metastatic progression (2). Biomarkers including the neutrophil, lymphocyte and platelet count, as well as the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and monocyte-lymphocyte ratio (MLR) are indices of inflammation (3). They have been reported to be prognostic factors in several types of solid tumor. The NLR is defined as neutrophil count divided by lymphocyte count. The prognostic value of the NLR has been confirmed in patients with colorectal cancer (4), hepatocellular carcinoma (5), BC (6), bladder cancer (7), lung cancer (8), pancreatic cancer (9), prostate cancer (10) and renal cell cancer (RCC) (11-13). The PLR is defined as the platelet count divided by the lymphocyte count. The prognostic value of PLR has been studied in patients with various cancer types (14), including gastric cancer (15), colorectal cancer (16), hepatocellular carcinoma (17), ovarian cancer (18), non-small cell lung cancer (19), pancreatic cancer (20), prostate cancer and RCC (21-24).

The LMR is the determined by dividing the lymphocyte count by the monocyte count in the blood. In turn, the MLR is the monocyte count divided by the lymphocyte count in the blood. The prognostic value of the LMR or MLR has been reported in patients with pulmonary squamous cell carcinoma (lung cancer) (25), hepatocellular carcinoma (26), colorectal...
cancer (27), endometrial cancer (28), pancreatic cancer (29),
gastric cancer (30) and ovarian cancer (31). An elevated pre-
treatment LMR was reported as a significant positive prog-
nostic factor for patients with locally advanced BC. According
to univariate and multivariate Cox regression analyses, elevated
LMR levels (≥4.25) were significantly associated with a favor-
able prognosis regarding disease-free survival (DFS) (32). In
line with this, a low pre-operative LMR was reported to be a
poor prognostic factor for BC patients (33). A prognostic role
of the NLR in BC patients has been determined by certain
studies (6,34). A higher pre-treatment peripheral NLR was
identified as a significant and independent poor prognostic
factor for BC and TNBC (34). Certain meta-analyses have
reported that the PLR may be a prognostic factor in BC patients.
Zhu et al (35), have demonstrated that a high PLR was associ-
ated with worse overall survival (OS) and DFS in BC patients.

The aim of the present study was to evaluate the prognostic
value of the PLR, NLR and the MLR in BC patients.

Patients and methods

Patients. The medical records and laboratory results of 436
BC patients who were diagnosed and treated at the MSC
Memorial Cancer Centre and Institute of Oncology, Gliwice
Branch (Gliwice, Poland) from January 2005 to June 2018 were
reviewed. The median age of the patients was 52.5 years (range,
25.2–78.3 years). All of the patients were women and had a good
overall performance status (ZUBROD 0–1) (normal activity or
symptomatic and ambulatory, cares for self) (36). All patients
provided written informed consent regarding the use of their
biological material for clinical research (all were routine labo-
ratory analyses). The blood cell parameters were determined
at the baseline, before first treatment. Treatment strategies are
shown in Table I. In retrospective analysis, patients with PLR
(>190.9) (P=0.026) and NLR (≥2.65) (P=0.025) significantly
more often had received chemotherapy regiments with taxanes.
Similarly, patients with elevated PLR (P=0.0001) and NLR
(P=0.042) more frequently had no surgery. In contrary, women
with lower PLR (P=0.006), NLR (P=0.015) or MLR (P=0.012)
were more frequently treated with hormonotherapy. In our
study, there was reported no association between radiotherapy
and PLR (P=0.359), NLR (P=0.981) or MLR (P=0.225).

Patients underwent clinical follow-up examinations every
three months in the first two years, then every six months until
the fifth year after diagnosis and every year thereafter. The
inclusion criteria were as follows: BC confirmed by microscopic
examination, performance status of ZUBROD 0–1, an age of
≥18 years, and renal and liver function as well as bone marrow
parameters within the normal ranges. The data, including the
age at diagnosis, menopausal status, treatment strategy, disease
stage according to the Tumor-Nodes-Metastasis classification,
tumor histology, estrogen (ER) and progesterone (PR) status,
were as well as the presence of HER2 overexpression and contralat-
eral BC, were gathered from hospital records and pathology
reports. The analysis of the patients' medical records was
performed according to national law regulations. The clini-
copathological characteristics of the patients are presented
in Table II.

The prognostic value (regarding OS) of various laboratory
parameters, including the PLR, NLR and MLR, was assessed
based on univariate and multivariate analysis. The cut-off
values were determined using receiver operating characteristic
curves. Based on the cut-off values determined, the NLR was
considered as 'elevated' at >2.65, the MLR value was 'elevated'
at >0.28 and the PLR was considered 'elevated' at >190.9.

Statistical analysis. Statistical analysis was performed using
Dell Statistica v.13 software. The frequency of the appear-
ance of side effects was denoted. Qualitative features were
presented as the percentage of their occurrence and evalu-
ated with Fisher's test and the Chi-squared test with Yates
correction. Continuous data were expressed as the median
(first quartile-third quartile) and the significance of differ-
cences was identified using the Mann-Whitney U-test. Survival
curves were obtained using the Kaplan-Meier method and the
log-rank test was performed to determine the significance
of differences in survival between subgroups. The relative
risk of death was estimated as hazard ratios (HRs) using
the Cox proportional hazard regression. NLR and PLR were
re-evaluated in multivariate analyses adjusted significant BC
prognostic factors. P<0.05 was considered to indicate a statisti-
cally significant difference.

Results

Follow-up. The median duration of follow-up was 71 months
(range, 3-156 months). The 5- and 10-year OS rates were 88.1
and 80.2%, respectively.

Patients characteristics according to NLR. Patients with an
NLR of >2.65 were more frequently of younger age (median
47.7 vs. 53.5 years, P=0.021) and more frequently had a nega-
tive ER(-) status (47 vs. 32%, P=0.008) in comparison with
the NLR ≤2.65 subgroup. There was no difference between
the NLR >2.65 and ≤2.65 groups with regard to tumor size
(78 vs. 71%; P=0.187), negative lymph node status (57 vs. 55%;
P=0.803) and BC subtype (P=0.242; Table II).

Prognostic value of an elevated NLR. The 5-year OS in the
NLR >2.65 subgroup was lower compared with that in the
NLR ≤2.65 subgroup (82.5 vs. 89.6%; P=0.053; Fig. 1A),
particularly in those patients with triple-negative breast cancer
(TNBC; 70.3 vs. 89.3%; P=0.034; Fig. 1B), in patients with
ER(-) status tumors (66.6 vs. 83.6%; P=0.018; Fig. 1C) or
with a higher tumor grade of G3 (77.4 vs. 89.0%; P=0.020;
Fig. 1D). Similar but insignificant association was observed
in subgroups with lymph node metastases (74.3 vs. 82.6%;
P=0.118; Fig. 1E) and HER2 overexpression (80.8 vs. 87.8%;
P=0.167; Fig. 1F).

Patients characteristics according to PLR. Patients with a
high PLR (>190.9) more frequently had a higher histological
tumor grade of G3 (54 vs. 37%; P=0.020), an ER(-) status
(52 vs. 32%; P=0.005) and TNBC (31 vs. 18%; P=0.028) in
comparison with those with a low PLR (Table II).

Prognostic value of an elevated PLR. The 5-year OS was lower
in patients with a PLR of ≥190.9 compared with that in patients
with a PLR of ≤190.9 (78.7 vs. 89.4%; P=0.020; Fig. 2A). A
PLR of >190.9 was also associated with a worse OS rate in
## Table I. Treatment strategy.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>All groups (n=436)</th>
<th>NLR ≤2.65 (n=346)</th>
<th>NLR &gt;2.65 (n=90)</th>
<th>P-value</th>
<th>PLR ≤190.9 (n=382)</th>
<th>PLR &gt;190.9 (n=54)</th>
<th>P-value</th>
<th>MLR ≤0.28 (n=275)</th>
<th>MLR &gt;0.28 (n=159)</th>
<th>P-value</th>
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<td>41 (12)</td>
<td>4 (4)</td>
<td>0.0498</td>
<td>43 (11)</td>
<td>2 (4)</td>
<td>0.088</td>
<td>30 (11)</td>
<td>15 (9)</td>
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<td>305 (88)</td>
<td>86 (96)</td>
<td></td>
<td>339 (89)</td>
<td>52 (96)</td>
<td></td>
<td>245 (89)</td>
<td>144 (91)</td>
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<td><strong>Chemotherapy regimen</strong></td>
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<td></td>
</tr>
<tr>
<td>Total n for all chemotherapy</td>
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<td>305</td>
<td>86</td>
<td>0.025</td>
<td>265 (78)</td>
<td>37 (71)</td>
<td>0.026</td>
<td>193 (79)</td>
<td>108 (75)</td>
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<td>241 (79)</td>
<td>61 (71)</td>
<td></td>
<td>265 (78)</td>
<td>37 (71)</td>
<td></td>
<td>193 (79)</td>
<td>108 (75)</td>
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<td>AC + taxanes</td>
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<td>24 (28)</td>
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<td>66 (19)</td>
<td>14 (27)</td>
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<td>47 (19)</td>
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<td>Mastectomy</td>
<td>278 (64)</td>
<td>224 (65)</td>
<td>54 (60)</td>
<td>0.042</td>
<td>246 (64)</td>
<td>32 (59)</td>
<td>0.0001</td>
<td>177 (64)</td>
<td>99 (62)</td>
<td>0.153</td>
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<td>Breast conservation surgery</td>
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<td>105 (30)</td>
<td>25 (28)</td>
<td></td>
<td>119 (31)</td>
<td>11 (20)</td>
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<td>85 (31)</td>
<td>45 (28)</td>
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<tr>
<td>Without surgery</td>
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<td>17 (5)</td>
<td>11 (12)</td>
<td></td>
<td>17 (4)</td>
<td>11 (20)</td>
<td></td>
<td>13 (5)</td>
<td>15 (9)</td>
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<tr>
<td><strong>Hormonotherapy</strong></td>
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<td></td>
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<td>0.006</td>
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<tr>
<td>No</td>
<td>149 (34)</td>
<td>108 (31)</td>
<td>41 (46)</td>
<td></td>
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<td>28 (52)</td>
<td></td>
<td>82 (30)</td>
<td>67 (42)</td>
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<tr>
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<td>287 (66)</td>
<td>238 (69)</td>
<td>49 (54)</td>
<td></td>
<td>261 (68)</td>
<td>26 (48)</td>
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<td>193 (70)</td>
<td>92 (58)</td>
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<td><strong>Radiotherapy</strong></td>
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<td>0.359</td>
<td></td>
<td></td>
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<tr>
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<td>88 (25)</td>
<td>23 (26)</td>
<td></td>
<td>100 (26)</td>
<td>11 (20)</td>
<td></td>
<td>75 (27)</td>
<td>35 (22)</td>
<td></td>
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<tr>
<td>Yes</td>
<td>325 (75)</td>
<td>258 (75)</td>
<td>67 (74)</td>
<td></td>
<td>282 (74)</td>
<td>43 (80)</td>
<td></td>
<td>200 (73)</td>
<td>124 (78)</td>
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</table>

Data are presented as n (%). AC, Adriamycin (or doxorubicin; 60 mg/m²) and Cyclophosphamide (600 mg/m²) treatment; FAC, Fluorouracil (500 mg/m²), Adriamycin (or doxorubicin; 50 mg/m²) and Cyclophosphamide (500 mg/m²) treatment; CMF, Cyclophosphamide (100 mg/m²), Methotrexate (40 mg/m²) and Fluorouracil (600 mg/m²) treatment.
Table II. Patient clinicopathological characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NLR ≤ 2.65 (n=346)</th>
<th>NLR &gt; 2.65 (n=346)</th>
<th>P-value</th>
<th>PLR ≤ 190.9 (n=382)</th>
<th>PLR &gt; 190.9 (n=54)</th>
<th>P-value</th>
<th>MLR ≤ 0.28 (n=275)</th>
<th>MLR &gt; 0.28 (n=159)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (Q1-Q3)</td>
<td>52.5 (44.2-60.8)</td>
<td>53.4 (45.0-61.0)</td>
<td>0.021</td>
<td>53.4 (44.9-61.1)</td>
<td>54.7 (42.6-65.7)</td>
<td>0.022</td>
<td>53.5 (45.0-60.7)</td>
<td>55.8 (43.1-61.7)</td>
<td>0.002</td>
</tr>
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<td>Menopausal status</td>
<td>0.021</td>
<td>0.035</td>
<td>0.186</td>
<td>0.021</td>
<td>0.035</td>
<td>0.186</td>
<td>0.021</td>
<td>0.035</td>
<td>0.186</td>
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<tr>
<td>Tumor size</td>
<td>0.021</td>
<td>0.035</td>
<td>0.186</td>
<td>0.021</td>
<td>0.035</td>
<td>0.186</td>
<td>0.021</td>
<td>0.035</td>
<td>0.186</td>
</tr>
<tr>
<td>Lymph node status</td>
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<td>0.035</td>
<td>0.186</td>
<td>0.021</td>
<td>0.035</td>
<td>0.186</td>
<td>0.021</td>
<td>0.035</td>
<td>0.186</td>
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<tr>
<td>Tumor grade</td>
<td>0.021</td>
<td>0.035</td>
<td>0.186</td>
<td>0.021</td>
<td>0.035</td>
<td>0.186</td>
<td>0.021</td>
<td>0.035</td>
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<tr>
<td>ER status</td>
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<td>0.035</td>
<td>0.186</td>
<td>0.021</td>
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<td>0.021</td>
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<td>ER status</td>
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<td>0.186</td>
<td>0.021</td>
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<td>0.186</td>
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<td>HER2 status</td>
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<td>0.186</td>
<td>0.021</td>
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<td>0.186</td>
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<td>Molecular subtype</td>
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<td>0.035</td>
<td>0.186</td>
<td>0.021</td>
<td>0.035</td>
<td>0.186</td>
<td>0.021</td>
<td>0.035</td>
<td>0.186</td>
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<tr>
<td>WBC (10^9 cells/l)</td>
<td>6.38 (5.18-7.59)</td>
<td>6.68 (5.57-7.76)</td>
<td>0.0001</td>
<td>6.32 (5.03-7.70)</td>
<td>6.80 (5.06-8.67)</td>
<td>0.0001</td>
<td>6.49 (5.49-7.70)</td>
<td>6.67 (5.65-8.27)</td>
<td>0.0001</td>
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<tr>
<td>Neutrophil count</td>
<td>3.45 (2.32-4.73)</td>
<td>3.65 (2.47-4.62)</td>
<td>0.0001</td>
<td>3.50 (2.40-4.66)</td>
<td>3.71 (2.54-4.76)</td>
<td>0.0001</td>
<td>3.45 (2.32-4.73)</td>
<td>3.71 (2.54-4.76)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>1.62 (1.10-2.35)</td>
<td>1.55 (1.05-2.13)</td>
<td>0.0001</td>
<td>1.69 (1.15-2.36)</td>
<td>1.55 (1.05-2.13)</td>
<td>0.0001</td>
<td>1.62 (1.10-2.35)</td>
<td>1.55 (1.05-2.13)</td>
<td>0.0001</td>
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<tr>
<td>Monocyte (10^9 cells/l)</td>
<td>0.49 (0.30-0.70)</td>
<td>0.58 (0.43-0.75)</td>
<td>0.003</td>
<td>0.49 (0.30-0.70)</td>
<td>0.58 (0.43-0.75)</td>
<td>0.003</td>
<td>0.49 (0.30-0.70)</td>
<td>0.58 (0.43-0.75)</td>
<td>0.003</td>
</tr>
<tr>
<td>Platelet (10^9 cells/l)</td>
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<td>260.5 (213.0-295.0)</td>
<td>0.0001</td>
<td>250.0 (217.0-292.0)</td>
<td>260.5 (213.0-295.0)</td>
<td>0.0001</td>
<td>250.0 (217.0-292.0)</td>
<td>260.5 (213.0-295.0)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Data are presented either as n (%) or median (Q1-Q3), as indicated. NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; T, tumor size; G, tumor grade; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.
the subgroups with TNBC (68.2 vs. 88.5%; P=0.032; Fig. 2B), ER(-) status tumors (57.7 vs. 83.6%; P=0.002; Fig. 2C) or tumors with a higher histological grade of G3 (70.4 vs. 89.2%; P=0.002; Fig. 2D), lymph node metastases (70.0 vs. 83.8%; P=0.085; Fig. 2E), tumors with HER2 overexpression (73.7 vs. 88.2%; P=0.061; Fig. 2F) and the non-Luminal BC subtype (43.6 vs. 74.8%; P=0.018) and the presence of BRCA mutation (61.4 vs. 81.6%; P=0.058).

Figure 1. Prognostic value of an elevated NLR in breast cancer patients. (A) All patients (P=0.053), (B) patients with triple negative BC (P=0.034), (C) patients with ER-negative (P=0.018), (D) patients with tumor grade G3 (P=0.020), (E) patients with nodal status positive (P=0.118) and (F) patients with HER2-positive (P=0.167). NLR, neutrophil-lymphocyte ratio; BC, breast cancer; ER, estrogen receptor.

Figure 2. Prognostic value of an elevated PLR in breast cancer patients. (A) All patients (P=0.020), (B) patients with triple negative BC (P=0.032), (C) patients with ER-negative (P=0.002), (D) patients with tumor grade G3 (P=0.002), (E) patients with nodal status positive (P=0.085) and (F) patients with HER2-positive (P=0.061). PLR, platelet-lymphocyte ratio; BC, breast cancer; ER, estrogen receptor.
Patients characteristics according to MLR. Patients with an elevated MLR (>0.28) more frequently had an ER(-) status (42 vs. 31%; P=0.031) compared with those with a lower MLR. There was no difference between the high and low MLR groups regarding the tumor size (73 vs. 76%; P=0.186), the presence of lymph node metastases (58 vs. 56%; P=0.345) and the frequency of a histological tumor grade G3 (40 vs. 39%; P=0.783; Table II).

Prognostic value of an elevated MLR. In the cohort of the present study, an ‘elevated’ MLR (>0.28) was not associated with OS time (P=0.830; Fig. 3A), also not in the subgroups with TNBC (P=0.219; Fig. 3B), ER(-) (P=0.453; Fig. 3C), G3 (P=0.995; Fig. 2D) and HER2 overexpression (P=0.474; Fig. 3F). However, a worse OS rate was observed in patients with lymph node metastases and an ‘elevated’ MLR (77.5 vs. 85.6%; P=0.058; Fig. 2E).

Univariate and multivariate analysis. Univariate Cox regression analyses of OS showed prognostic significance for factors such as patient’s age [hazard ratio (HR)=1.03; 95% confidence interval (CI): 1.00-1.05; P=0.018], tumor size (T3-4 vs. T1-2, HR=2.75; 95% CI: 1.69-4.48; P=0.0001), the presence of lymph node metastases (N+ vs. N0, (HR=3.74; 95% CI: 2.17-6.46; P=0.0001), estrogen receptor status (ER(+) vs. ER(-), HR=0.51; 95% CI: 0.32-0.83; P=0.007) and PLR (PLR>190.9 vs. ≤190.9, HR=2.02; 95% CI: 1.12-3.65; P=0.020). Factors such as menopausal status, tumor grade, HER2 overexpression, NLR and MLR were not statistically significant (Table III).

Multivariate analysis revealed that the NLR and PLR are insignificant negative prognostic factors in all BC patients (Table III). Negative prognostic factors were: Patients age, tumor size and lymph node metastases. In contrary, positive prognostic factor was positive steroid receptor status (ER+). However, analysis of the subgroup of patients with ER(-) tumors indicated that a higher NLR (HR=2.40; 95% CI: 1.20-4.80; P=0.013) and a higher PLR (HR=2.51; 95% CI: 1.23-5.14; P=0.012) were independent prognostic factors for a lower OS together with metastatic lymph nodes (HR=5.47; 95% CI: 2.46-12.15; P=0.0001 and HR=4.82; 95% CI: 2.15-10.78; P=0.0001, respectively; Table IV).

Discussion

In this retrospective study, we reported the prognostic value of the NLR, PLR and MLR in BC patients. The influence of the NLR, PLR and PLR on the survival time (OS or DFS) of BC patients has been investigated in numerous studies (6,34,35).

In the present study, no association between an elevated MLR (>0.28) and the OS time was identified (P=0.830), also not in the subgroups with TNBC (P=0.219) and ER(-) status (P=0.453). An elevated pre-treatment (prior to neoadjuvant chemotherapy) peripheral blood LMR was reported to be a significantly favorable prognostic factor for patients with locally advanced BC. Univariate and multivariate analysis confirmed that a higher LMR (≥4.25) was significantly associated with favorable DFS (P = 0.009 and P = 0.011, respectively). In addition, univariate analysis revealed an increased probability of DFS in patients with a higher lymphocyte count (≥1.5x10^9/l). However, a lower monocyte count (<0.4x10^9/l) was associated with a significantly better prognosis regarding DFS (P=0.010) (32). The pre-operative LMR (prior to neoadjuvant chemotherapy) as a prognostic factor in BC patients was also analyzed in a meta-analysis by Hu et al (33), revealing that a low LMR was...
significantly associated with a worse prognosis regarding OS (HR=0.65; 95% CI: 0.47-0.90; P=0.009) and DFS (HR=0.60; 95% CI: 0.49-0.74; P<0.001). Subgroup analyses indicated that a low LMR had a negative impact on the prognosis regarding OS in Asian populations with triple-negative BC without metastases. However, no association between a low LMR and clinicopathological factors was identified ([33]). Our data did not confirm above mentioned results. In our study MLR was not a prognostic factor according to OS, also in subgroup analysis. However, we did not analyze DFS.

In the present study, a higher NLR was associated with a lower 5-year OS rate, particularly in the subgroup of TNBC (P=0.034), in patients with ER(-) status tumors (P=0.001) and in patients with G3 (P=0.020). Similar but insignificant association was observed in subgroups with lymph node metastases (P=0.118) and HER2 overexpression (P=0.167). In a previous study, Chen et al ([6]) suggested that a higher NLR may be a prognostic factor regarding OS with an HR of 2.28 (95% CI: 1.08-4.80; P heterogeneity<0.001), particularly in Caucasian populations (HR=4.53; 95% CI: 3.11-6.60; P heterogeneity=0.096). An elevated NLR was also associated with a high risk regarding DFS (HR=1.38; 95% CI=1.09-1.74; P heterogeneity=0.050) ([36]). In an analysis conducted by Jia et al ([34]), a higher pre-treatment level of NLR (before neo-adjuvant chemotherapy) was identified as a significant and independent poor prognostic factor for BC patients, particularly in the TNBC subgroup. The higher NLR was a better prognostic factor in comparison to a lower LMR. Univariate analysis indicated that a lower NLR (≤2.0) and a higher LMR (>4.8) were significantly associated with a better DFS in TNBC patients (P=0.007 and 0.011, respectively). By contrast, in other molecular BC subtypes (luminal subtype: ER+ and/or PR+ and HER2-; HER2-positive subtype: Table III. Univariate and multivariate analysis in all breast cancer patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>NLR Multivariate analysis</th>
<th>PLR Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95%CI)</td>
<td>P-value</td>
<td>HR (95%CI)</td>
</tr>
<tr>
<td>Age</td>
<td>1.03 (1.00-1.05)</td>
<td>0.018</td>
<td>1.03 (1.01-1.06)</td>
</tr>
<tr>
<td>Status postmenopausal vs. pre</td>
<td>1.36 (0.83-2.22)</td>
<td>0.218</td>
<td></td>
</tr>
<tr>
<td>T3-T4 vs. T1-T2</td>
<td>2.75 (1.69-4.48)</td>
<td>0.0001</td>
<td>1.97 (1.17-3.31)</td>
</tr>
<tr>
<td>N+ vs. N0</td>
<td>3.74 (2.17-6.46)</td>
<td>0.0001</td>
<td>3.65 (2.09-6.37)</td>
</tr>
<tr>
<td>G3 vs. G1-G2</td>
<td>1.27 (0.77-2.09)</td>
<td>0.344</td>
<td></td>
</tr>
<tr>
<td>ER(+) vs. ER(-)</td>
<td>0.51 (0.32-0.83)</td>
<td>0.007</td>
<td>0.53 (0.32-0.89)</td>
</tr>
<tr>
<td>HER2 positive vs. HER2 negative</td>
<td>1.56 (0.97-2.54)</td>
<td>0.069</td>
<td></td>
</tr>
<tr>
<td>NLR&gt;2.65 vs. NLR&lt;2.65</td>
<td>1.70 (1.00-2.90)</td>
<td>0.050</td>
<td>1.58 (0.92-2.72)</td>
</tr>
<tr>
<td>PLR &gt;190.9 vs. PLR ≤190.9</td>
<td>2.02 (1.12-3.65)</td>
<td>0.020</td>
<td></td>
</tr>
<tr>
<td>MRL&gt;0.28 vs. MRL ≤0.28</td>
<td>0.94 (0.56-1.58)</td>
<td>0.829</td>
<td></td>
</tr>
</tbody>
</table>

NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; HR, hazard ratio; CI, confidence interval; T, tumor size; N, node; G, tumor grade; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; MLR, monocyte to lymphocyte ratio.

Table IV. Multivariate analysis of the subgroup of patients with ER negative and grade G3 tumors.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>NLR Multivariate analysis</th>
<th>PLR Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95%CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Patients with ER negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N+ vs. N0</td>
<td>5.47 (2.46-12.15)</td>
<td>0.0001</td>
</tr>
<tr>
<td>NLR &gt;2.65 vs. ≤2.65</td>
<td>2.40 (1.20-4.80)</td>
<td>0.013</td>
</tr>
<tr>
<td>PLR &gt;190.9 vs. ≤190.9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Patients with tumor grade G3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3-T4 vs. T1-T2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>N+ vs. N0</td>
<td>4.04 (1.73-9.40)</td>
<td>0.001</td>
</tr>
<tr>
<td>ER(+) vs. ER(-)</td>
<td>0.28 (0.12-0.68)</td>
<td>0.005</td>
</tr>
<tr>
<td>NLR &gt;2.65 vs. ≤2.65</td>
<td>2.14 (0.97-4.68)</td>
<td>0.058</td>
</tr>
<tr>
<td>PLR &gt;190.9 vs. ≤190.9</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; HR, hazard ratio; CI, confidence interval; T, tumor size; N, node; ER, estrogen receptor.
HER2+), no significant association between the NLR or the LMR with survival (DFS or OS) was identified (34). Our study support the results of previous dates. We confirm NLR to be negative prognostic factor, especially for subgroups with TNBC, ER negative status or G3 tumors. In study conducted by Li et al (37) NLR in healthy people was positively associated with age. There was reported the highest NLR in the eldest age group. In contrary, the youngest age group had the lowest NLR. NLR was also slightly positively associated with blood pressure, and BMI (P<0.001). In our group, patients with an NLR of ≥2.65 were more frequently of younger age (median 47.7 vs. 53.5 years, P=0.021).

Another hematological parameter examined as a prognostic factor in BC patients is the PLR. In the present study, a lower 5-year OS in patients with PLR>190.9 in comparison with those with PLR≤190.9 was observed, particularly in the subgroup with TNBC (P=0.032) and in those patients with ER(-) status tumors (P=0.002) and in those patients with G3 (P=0.002). A meta-analysis conducted by Zhu et al (35), revealed that the PLR is an unfavorable prognostic factor in BC patients. In that study, a higher PLR was associated with a worse OS (HR=1.55; 95% CI: 1.07-2.25; P=0.022) and DFS (HR=1.73; 95% CI: 1.3-2.3; P<0.001) in BC patients. An elevated PLR was associated with worse OS in Asian populations and with poor DFS in Asian as well as non-Asian subgroups. In addition, PLR was identified as a significant prognostic factor for OS (HR=1.78; 95% CI: 1.06-2.99; P=0.03) and DFS in patients who receive chemotherapy (HR=2.6; 95% CI=1.47-4.61; P=0.001). Furthermore, the study reported an association between PLR and the presence of HER-2 overexpression (odds ratio=1.48; 95% CI: 1.2-1.83; P<0.001) (35). Results of our study confirm the role of elevated PLR as a negative prognostic factor in BC patients, particularly in the subgroups with TNBC, ER(-) status tumors or tumors with a higher histological grade of G, lymph node metastases, tumors with HER2 overexpression and the non-Luminal BC subtype and the presence of BRCA mutation.

An elevated pre-treatment NLR (>2.65) (insignificantly) and PLR (>190.9) (significantly) was associated with a worse prognosis regarding OS in BC patients. In univariate analysis higher NLR and PLR were significantly negative prognostic factors for subgroups such as: TNBC, ER(-) and with a higher tumor grade of G3. However, the MLR did not affect OS. In multivariate analyses in the ER(-) subgroup of patients, an elevated NLR and PLR were significant independent prognostic factors.

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Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Authors' contributions

JH analyzed and interpreted the patients' data and was a major contributor in writing the manuscript. ZK performed the statistical analyses, and analyzed and interpreted the data.

Ethics approval and consent to participate

At the time of venous blood collection for genetic diagnostic testing, all patients provided written informed consent. The present study analyzed the results of these genetic diagnostic tests retrospectively.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References