Inflammatory blood markers as prognostic and predictive factors for pathological complete response and toxicity in early breast cancer patients receiving neoadjuvant chemotherapy

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THESE

Pour obtenir le titre de
DOCTEUR EN MEDECINE

Présentée et soutenue publiquement
Par
Iléana CORBEAU
le 4 Octobre 2019

INFLAMMATORY BLOOD MARKERS AS PROGNOSTIC AND PREDICTIVE FACTORS FOR PATHOLOGICAL COMPLETE RESPONSE AND TOXICITY IN EARLY BREAST CANCER PATIENTS RECEIVING NEOADJUVANT CHEMOTHERAPY

Directeur de thèse : Madame le Dr Séverine GUIU

JURY

Président : Monsieur le Professeur Marc YCHOU

Assesseurs :
Madame le Professeur Nadine HOUEDE
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Aux membres du jury,

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PREAMBULE

Ce travail est constitué de deux articles, soumis pour publications dans « Breast Cancer Research an Treatment » et dans « Critical Reviews in Oncology / Hematology » respectivement. Il est accompagné d'une introduction et d'une conclusion en français.

Introduction générale

Le cancer du sein est le cancer le plus fréquent et la première cause de décès par cancer chez la femme (1). La mortalité par cancer du sein a diminué ces dernières années. Ceci est expliqué d'une part, par l'amélioration de la prise en charge thérapeutique, et d'autre part, par un diagnostic plus précoce lié au développement du dépistage en France. Plusieurs critères clinico-pathologiques sont utilisés pour déterminer si un cancer du sein est à priori de bon ou de mauvais pronostic, et déterminer si un traitement systémique adjuvant doit être administré (chimiothérapie, hormonothérapie), afin de diminuer le risque de récidive et de décès. Un facteur pronostique va permettre, en l'absence de traitement, de prédire l'évolution de la maladie en termes de risque de rechute et de décès (survie). Un facteur prédictif va permettre de prédire l'évolution de la maladie sous traitement et d'orienter une décision thérapeutique (réponse, toxicité). Les facteurs pronostiques classiques du cancer du sein sont : l'âge au diagnostic, le type histologique, la taille tumorale, le statut ganglionnaire, le grade histopronostique, la présence d'emboles péri-tumoraux, le statut des récepteurs hormonaux, le statut HER2 (Human Epidermal Growth Factor 2) et le Ki67. Indépendamment de leur valeur pronostique, les statuts des récepteurs hormonaux et de HER2 sont des facteurs prédictifs du bénéfice clinique apporté par l'hormonothérapie et les thérapies anti-HER2 comme le trastuzumab.

Il est cependant toujours difficile de pouvoir distinguer avec fiabilité les patients qui auront un vrai bénéfice d'un traitement systémique adjuvant, des patients qui n'auront pas d'amélioration de leur pronostic avec un tel traitement, qui sera par ailleurs potentiellement générateur de toxicité et de surcoût pour la société. La recherche de facteurs pronostiques et prédictifs est donc un enjeu majeur dans cette situation. En situation néoadjuvante il est également indispensable de disposer de facteurs prédictifs de réponse histologique complète, parfois corrélée à la survie notamment dans les cancers du sein triple négatifs et HER2 positifs (2).

Les marqueurs biologiques de l'inflammation, tels que les taux de globules blancs, de lymphocytes, de polynucléaires neutrophiles, de plaquettes ou bien des ratios tels que le ratio de neutrophiles sur lymphocytes (neutrophil to lymphocyte ratio, NLR) ou le ratio de plaquettes sur lymphocytes (platelets to lymphocyte ratio, PLR) pourraient être des

marqueurs pronostiques et / ou prédictifs dans de nombreux cancers, y compris dans le cancer du sein. De nombreuses études ont évalué ces biomarqueurs que ce soit en situation néo-adjuvante, adjuvante ou métastatique mais les résultats divergent (3–9).

Le rôle de l'inflammation dans l'initiation et le développement de cancers est de plus en plus étudié et il a été démontré que, les polynucléaires neutrophiles notamment, y participent à travers leur capacité à favoriser la néo-angiogenèse, à sécréter des métalloprotéines et à activer des facteurs de transcription tels que STAT3 (Signal Transducer and Activator Transcription 3) (10–15).

Dans ce travail de thèse nous nous sommes intéressés à ces marqueurs biologiques de l'inflammation et leur potentiel rôle en tant que marqueur pronostique et / ou prédictif de réponse à la chimiothérapie ou de risque de toxicité chimio-induite, et notamment le risque de neutropénie fébrile.

Nous vous présentons ici deux articles. Le premier est une étude rétrospective, sur une population de patientes présentant un cancer du sein localisé traitées à l'Institut du Cancer de Montpellier, ayant reçu une chimiothérapie néoadjuvante entre 2005 et 2013. Nous avons évalué si les différents marqueurs biologiques de l'inflammation cités ci-dessus pouvaient être : des facteurs pronostiques de survie (survie sans progression et survie globale), des facteurs prédictifs de la réponse histologique après chimiothérapie ou des facteurs prédictifs du risque de neutropénie fébrile.

Le deuxième article est une revue exhaustive de la littérature portant sur le NLR en tant que facteur pronostique et / ou prédictif dans le cancer du sein. La première partie collige les différents articles étudiant le NLR en tant que facteur pronostique. Nous avons différencié les articles portant sur les cancers du sein localisés (recevant une chimiothérapie néoadjuvante d'une part et un traitement adjuvant d'autre part), des articles portant sur les cancers du sein métastatiques. Nous avons également comparé les différents articles évaluant le NLR comme facteur prédictif de réponse histologique après chimiothérapie néoadjuvante. Enfin la dernière partie de ce second article rapporte les différents articles étudiant le NLR en tant que facteur prédictif de toxicité de la chimiothérapie.

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Article 1

Inflammatory blood markers as prognostic and predictive factors in early breast cancer patients receiving neoadjuvant chemotherapy

Evaluation des marqueurs biologiques de l'inflammation en tant que facteurs pronostiques et prédictifs chez les patientes recevant une chimiothérapie néoadjuvante pour un cancer du sein localisé.

Iléana CORBEAU, Simon THEZENAS, Aurélie MARAN-GONZALES, Pierre-Emmanuel COLOMBO, William JACOT, Séverine GUIU

ABSTRACT

Purpose: Inflammatory blood markers such as neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have been reported as putative prognostic factor for survival and predictive factor for pathological complete response (PCR) and toxicity in cancers, however with conflicting results.

Methods: We retrospectively analyzed data of 280 patients with early breast cancer receiving neo-adjuvant chemotherapy between 2005 and 2013 in our center. Neutrophil count, lymphocyte count and platelet count before treatment were collected as well as data on PCR, toxicity, recurrence and survival. Univariate and multivariate analyses were performed using a logistic regression model.

Results: In multivariate analysis, high PLR was found to be an independent prognostic factor for relapse-free survival (Hazard Ratio [HR] = 1.91; 95%CI = 1.15-3.16; p = 0.012) and shorter overall survival (HR = 1.83; 95%CI = 1.03-3.24; p = 0.039). NLR was an independent predictive factor for febrile neutropenia (HR = 0.28; 95%CI = 0.13-0.58; p = 0,001). No inflammatory blood marker was found to be predictive for PCR in the overall population, however when focusing on triple negative breast cancer molecular subtype, low white blood cell count (< 6.75 G/L) was predictive for a higher PCR rate (Odds ratio [OR] = 0.29; 95%CI = 0.14-0.61; p < 0.01).

Conclusion: In the present study, PLR was found as an independent prognostic factor for survival, while NLR was an independent predictive factor for febrile neutropenia. These results, if confirmed in prospective studies, could help tailoring treatment and supportive care in clinical routine practice considering their daily routine biological analysis nature.

Keywords: breast cancer, neoadjuvant chemotherapy, inflammatory blood marker, predictive factor, prognostic factor, pathological complete response

INTRODUCTION

Breast cancer (BC) is the most common feminine cancer (with over 2 million new cases worldwide in 2018) and the leading cause of cancer-related death in women (1). Although more and more patients undergo BC treatment, the mortality rate has decreased in developed countries due to improvement in treatments and early detection. Today's challenge is not only to cure these patients but also to reduce treatment-related toxicity.

Neo-adjuvant chemotherapy (NACT) has increasingly become used in early breast cancer (EBC) treatment, especially for patients with Her2 positive or triple negative breast cancer (TNBC). It allows the evaluation of the pathological response to chemotherapy, which has been shown to be correlated with survival (2) since patients achieving pathological complete response (PCR) are showing improved OS and RFS (3,4).

Inflammatory blood markers (IBM) have emerged as potential prognostic factors for survival in different types of cancers including BC, as well as predictive factors for histological response after NACT (5–11). IBM include leucocyte count, lymphocyte count, neutrophil count, and ratios such as platelet to lymphocyte ratio (PLR) or neutrophil to lymphocyte ratio (NLR), the last one being the most evaluated. Several studies have been published on IBM as predictive for PCR in EBC patients receiving NACT, however with conflicting results (12,13).

In the present study, we evaluated if IBM are prognostic for relapse-free survival (RFS) and / or overall survival (OS) in a large series of homogeneously treated EBC patients receiving sequential anthracycline – taxane NACT, and if these IBM are predictive for PCR in the same population of patients. We also evaluated if there was a correlation between IBM and NACT-related toxicity.

METHODS

Patients

Patients treated with NACT for an EBC in our institution between January 2005 and September 2013 were included in a clinico-pathological database (14–16). The database follow-up has been updated and completed until March 2019. Patients included in our study presented with unilateral, unifocal, non-metastatic EBC confirmed by core needle biopsy and had received sequential anthracycline – taxane NACT. Initial blood samples were collected before starting

any treatment. Patients without available initial blood sample analysis were excluded from the present study.

Pathological assessments

Hormone receptor positive BC were defined as tumors with ≥ 10% of estrogen and/or progesterone receptors immunohistochemical (IHC) expression. Her2 positive BC were defined as tumors with Her2+++ on IHC staining or tumors with IHC Her2++ expression and average HER2 gene copy numbers ≥ 6 at cases with a HER2/CEP17 ratio of less than 2 or a HER2/CEP17 ratio of 2 or more, independently of the average gene copy number after fluorescent *in situ* hybridization (FISH) (17).

Treatments

All patients received three to four cycles of anthracycline-based chemotherapy, followed by three to four cycles of taxane (weekly paclitaxel or docetaxel every 3 weeks). Patients with Her2 positive tumors received neoadjuvant trastuzumab concomitantly with taxane, followed by adjuvant trastuzumab for a total of 12 months. Patients with hormone receptor positive received adjuvant hormone therapy for 5 years. All patients received adjuvant radiation therapy according to ESMO guidelines (18).

Endpoints

PCR was defined as absence of invasive cancer in the breast and axillary nodes, irrespective of the presence of *in situ* ductal carcinoma (ypT0/is ypN0). RFS was defined as the time from the date of biopsy to the date of documented relapse (local, loco-regional or distant recurrence) or death for progression. OS was defined as the time from the date of biopsy to the date of documented death from any cause.

For the toxicity endpoint, febrile neutropenia (FN) was defined as temperature ≥ 38.5° and neutrophil count ≤ 0.5 G/L (19).

As no standard definition of relevant IBM is available, different cut-offs for NLR and PLR were tested. First, a cut-off was set using receiver operating characteristic (ROC) curves, a second one was based using the cut-offs previously published (20–25). We also calculated a cut off for NLR to be statistically associated with a risk of FN.

Statistical analysis

Descriptive analyses were performed using median and range for continuous parameters, frequency and percentage for categorical variables.

Baseline characteristics of included patients were compared by Kruskal-Wallis tests or Wilcoxon for continuous variables, or chi2 or Fisher exact test for categorical variables.

The median follow-up was calculated using the reverse Kaplan-Meier method with its confidence interval (CI) of 95%. All event free survival (RFS, OS) were estimated using the Kaplan-Meier method, and then described using medians and rates with their associated 95% CI.

Survival curves were drawn, and the log-rank test was performed to assess differences between groups.

Moreover, multivariate analyses were carried out using logistic regressions or Cox's proportional hazards regressions, with a stepwise selection procedure, to investigate known predictive or prognostics factors respectively.

Odds ratios (OR) and hazard ratios (HR) with their 95% CIs are presented to display reductions of risk.

ROC curves were used to discriminate the optimal threshold for individual marker (NLR / PLR) calculated to maximize the Youden's index (gold standard: relapse).

All P values reported are two sided, and the significance level was set at 5% ($p < 0.05$). Statistical analysis was performed using the STATA 13.1 software (Stata Corporation, College Station, TX, USA).

RESULTS

Patient's characteristics

Two hundred and eighty patients were included in the present study. The median age at diagnosis was 50.3 years old and 36.8% of our patients were menopaused at diagnosis. Clinical stage was mainly cT2 (58.9%) and half of the patients (51.8%) had clinical lymph node invasion. Majority of patients were affected by an invasive ductal carcinoma (84.0%) and histological grade 3 disease (52.2%). One hundred and twenty-seven patients (45.4%) had hormone receptor positive / Her2 negative BC, 41 patients (14.6%) had hormone receptor positive /

Her2 positive BC, 40 patients (14.3%) had hormone receptor negative / Her2 positive BC and 72 patients (25.7%) had TNBC. Eleven patients (6.3%) were known to be *BRCA* 1 or 2 deleterious mutation carriers.

Before any treatment, median white blood cell count was 6.8 G/L, median lymphocyte count was 1.9 G/L, median neutrophil count was 3.9 G/L, median NLR was 2.0 and median PLR was 132.3. Patients' clinical and biological characteristics are summarized in Table 1.

Ninety-one percent of the patients completed the planned NACT sequence. Main causes of interruption were toxicity (3.9%) and progression (1.4%). Seventy percent of the patients had breast-conserving surgery and 98.9% had lymph node surgery. Ninety-seven percent of patients received adjuvant radiation therapy, 55.7% of patients received adjuvant hormone therapy (for reminder 60% of patients were affected by a hormone receptor positive BC) and 27.9% received neoadjuvant / adjuvant trastuzumab (28.9% had Her2 positive BC).

Cut-offs for NLR and PLR calculated using ROC curves gave 2.4 and 131.1 cut-off values, with AUC-ROC values of 0.55 and 0.58 respectively. These cut-offs were not associated with any significant predictive or prognostic value (except for PLR and RFS but only in univariate analysis) (data not shown). Therefore, we used previously published cut-offs for NLR and PLR at 2 and 150 respectively, according to the literature (20–22,26–28).

<u>Predictive factors for PCR (Table 2)</u>

Seventy-four patients (26.4%) patients reached PCR. In univariate analysis, histological grade ($p = 0.001$), mitotic index ($p = 0.006$), hormone receptor expression ($p < 0.001$) and molecular subtype ($p < 0.001$) were correlated with PCR. None of the IBM was significantly correlated to PCR. In multivariate analysis, nodal status (OR = 0.43; 95%CI = 0.23-0.82; $p = 0.01$), histological grade (grade 2: 0R = 0.13; 95%CI = 0.07-0.27; $p < 0.01$ and grade 3: OR = 0.28; 95%CI = 0.12-0.63; $p<0.01$ versus grade 1) and molecular subtype (hormone receptor positive / Her2 positive: OR = 7.98; 95%CI = 0.12-0.63; $p < 0.01$; hormone receptor negative / Her2 positive: OR = 11.94; 95%CI = 4.76-29,91; $p > 0.01$ and hormone receptor negative / Her2 negative: OR = 4.65; 95%CI = 1.98-10.89; $p < 0.01$; compared to hormone receptor positive / Her2 positive) were independent predictive factors of PCR.

<u>Prognostic factors for RFS (Table 3)</u>

With a median follow-up of 6.7 years (range 0.2 to 11.3) at the date of data cleaning (March 2019), 65 patients (23.2%) had relapsed, including 51 patients with metastatic relapse and 14 patients with locoregional relapse.

Higher cT stage (p = 0.005), inflammatory BC (p = 0.003), hormone receptor negative BC (p = 0.003), TNBC (p = 0.001), not reaching PCR (p = 0.009), low neutrophil count (< 1.5G/L) (p = 0.007), and high PLR (≥ 150) (p = 0.044) were all correlated to a higher risk of relapse in univariate analysis.

In multivariate analysis, high PLR was still an independent prognostic factor (HR = 1.91; 95%CI = 1.15-3.16; p = 0.012) as well as low neutrophil count (<1.5 G/L) (HR = 0.06; 95%CI = 0.03-0.12; p < 0.001). Other independent prognostic factors for RFS were high tumor size (HR = 2.07; 95%CI = 1.26-3.39; p = 0.004), TNBC subtype (HR = 4.11; 95%CI = 2.28-7.42; p < 0.001) and PCR achievement (HR = 0.27; 95%CI = 0.12-0.56; p = 0,001).

Prognostic factors for OS (Table 4)

At the end of follow-up, 51 patients (18.2%) had died, including 40 BC-related deaths. Other deaths were due to a second cancer for 6 patients, chemotherapy related toxicity (cardiac failure) for one patient, intercurrent disease for one patient and unknown for 3 patients.

In univariate analysis, the following factors were correlated to a poor survival: higher tumor size (p = 0.006), inflammatory BC (p = 0.014), hormone receptor negative BC (p = 0.001), TNBC (p < 0.001), not reaching PCR (p = 0.041) and platelet count ≥ 264 G/L (p = 0.049).

In multivariate analysis, high PLR and low neutrophil count (< 1.5 G/L) were associated to shorter OS (HR = 1.83; 95%CI = 1.03-3.24; p = 0.039 and HR = 0.12; 95%CI = 0.06-0.24; p < 0.001, respectively). Other independent prognostic factors for OS were high tumor size (HR = 2.43; 95%CI = 1.37-4.30; p = 0.002), TNBC subtype (HR = 6.59; 95%CI = 3.34-13.01; p < 0.001) and PCR achievement (HR = 0.29; 95%CI = 0.13-0.66; p = 0.003).

Sub group analyses

Platelet count, neutrophil count, lymphocyte count, PLR or NLR were not predictive factors for PCR in any of the molecular subtypes. Low white blood cell count (< 6.75 G/L) was an independent predictive factor for PCR in patients with TNBC (OR = 0.29; 95%CI = 0.14-0.61; p

< 0.01); but not for other molecular subtypes. Data for survival were not mature enough to highlight prognostic factors according to the molecular subtype.

Predictive factors for febrile neutropenia (Table 5)

Thirty-eight patients (13.6%) patients developed FN during NACT. Post-menopausal status (p = 0.005), negative hormone receptor (p = 0.003), low platelet count (< 264 G/L) (p = 0.015), low white blood cell count (< 6.75 G/L) (p = 0.002) and low NLR (p = 0.001) were predictive for FN in univariate analysis. Molecular subgroup was predictive for since 34.9% of positive hormone receptor-Her2 negative patients developed FN, 32.6% of negative hormone receptor-Her2 negative patients developed FN, 27.9% of negative hormone receptor-Her2 positive patients developed FN and only 4.7% of patients with positive hormone receptor and positive Her2 status developed FN (p = 0.007).

In multivariate analysis, low NLR was independently predictive for FN (OR = 0.28; 95%CI = 0.13-0.58; p = 0,001) as well as low platelet count (< 264 G/L) and low white blood cell count (< 2.75 G/L) (OR = 0.40; 95%CI = 0.21-0.75; p = 0.004 and OR = 0.35; 95%CI = 0.17-0.72; p = 0.004, respectively). Clinical tumor size was also a predictive factor for FN (OR = 0.43; 95%CI = 0.20-0.91; p = 0.028). Patient with positive hormone receptor and positive Her2 status developed less FN than patients with positive hormone receptor and negative Her2 status (OR = 0.21; 95%CI = 0.005-0.93; p = 0.039). Other molecular subtypes were not independently associated with FN.

We also calculated a cut-off for NLR to be predictive for FN, this cut-off point was set at 4.125, meaning that patients with an initial NLR higher than 4.125 had fewer risk of FN (AUC = 0.52; p = 0.308). Seventeen patients (6.1%) had NLR ≥ 4.125 and the risk of FN for this group was 1.4%. Two hundred and sixty-three patients (93.1%) had NLR lower than 4.125 and the risk of FN for this group was 13.9%.

DISCUSSION

We report here the correlations between IBM and clinical endpoints in a homogeneous population of 280 BC patients treated with NACT in a single institution. We showed that PLR is an independent prognostic factor for RFS and OS and that NLR is an independent predictive

factor for FN. None of the IBM were predictive for PCR in our overall population. When focusing on specific molecular subtypes, white blood cell count was an independent predictive factor for PCR in TNBC. In addition, as previously reported (3,4) we found a highly significant correlation between PCR and survival, PCR being prognostic both for RFS and OS in univariate and multivariate analyses in our study.

This is the second largest cohort of patients published regarding IBM as predictive factor (after Graziano *et al*'s study (29)) and the largest population with reported multivariate results regarding IBM as prognostic factor in patients with localized BC homogeneously receiving NACT. Our population is representative for patients receiving NACT since most of our patients were affected by cT2 stage (or higher), node positive BC. We chose to include the four molecular subtypes in order to have a comprehensive evaluation of the correlations between IBM and NACT in BC patients.

Most of the studies evaluating IBM as prognostic factor studied Asian-based populations (9,20,22,24,27,28,30–41) where use of anti-cancer drugs, particulary trastuzumab is inconsistently reported, inducing heterogeneity in survival expectations. This demographic variable could be associated with specific molecular and pharmacological features that can induce differences in toxicity and efficacy profiles. We report here a large population of western BC patients receiving sequential anthracycline and taxane-based chemotherapy, with access to anti-Her2 therapies.

Another strength of our series is the long clinical follow-up, with a median duration of more than 6 years, a substantially longer follow-up than most of the similar studies, allowing a relevant and mature evaluation of survival data.

Finally, we are the first ones to evaluate the relation between IBM and toxicity in a population of EBC patients receiving NACT and we found that low NLR was an independent predictive factor for FN.

One limitation comes from the monocentric, retrospective nature of our studied population. However, the clinicopathological characteristics of our population and our results are consistent with previously published studies evaluating IBM. In a closely-related population of BC patients receiving adjuvant treatment, Ramos Esquivel *et al* (42), Takeuchi *et al* (24) and Cho *et al* (36) also showed that PLR was a prognostic factor for disease-free survival (DFS) and

OS in univariate and multivariate analyses. In a population of patients with metastatic TNBC, Vernieri *et al* (43), found that PLR was statistically significantly associated to progression-free survival. Only one study (written by Losada *et al (44)*) evaluating PLR as prognostic factor in patients receiving NACT failed to show evidence of a relation between PLR and DFS. Therefore, their population was different from ours since they included only elderly patients (≥ 65 years old).

Results on NLR and survival are more controverted. In population receiving NACT, two studies (Suppan *et al* (45), and Marin Hernandez *et al* (46)) found, similarly to us, that NLR was not prognostic for DFS and / or OS, whereas two other studies (Chen *et al* (20), and Koh *et al* (31)) found that NLR was associated with survival. These conflicting results could be due to a difference in the studied population since both Chen *et al* and Koh *et al* had fewer or none TNBC patients in their studied population, while Suppan *et al,* Marin Hernandez *et al* and our study included over 20% of TNBC patients. NLR prognostic value appears more clearly validated in the population of patients receiving adjuvant chemotherapy, since many studies have demonstrated a significant correlation in this setting (22,23,28,32,34,37,39,41,47–50).

In our population, we found no significant correlation between NLR nor PLR with PCR, concordantly with previous reports (26,29,30,44,45), evaluating a similar population of BC patients receiving NACT. Only one study (Chae *et al* (27)) found that NLR was predictive for PCR, however, they included only Chinese patients with TNBC, differing strikingly from our population. Cuello Lopez *et al* (51) reported, in univariate analysis, that patients with low PLR had higher PCR rates, but no multivariate data were available in this publication.

As previously said, we are the first study, to our knowledge, to analyze data on the correlations between IBM and chemotherapy-related toxicity in BC patients receiving NACT. Evaluation of IBM, accessible through a simple blood analysis, could appear as an interesting, inexpensive tool to individualize one's hematological risk under NACT. Considering NLR as a predictive factor for FN could help to decide, for example, which patients should benefit from granulocyte colony stimulating factors in intermediate risk situations (52). The only data available on NLR and toxicity in this situation were published by Yamanouchi *et al* (53) and they found no significant correlation. However, the population was limited (67 metastatic BC patients), possibly explaining the lack of statistical significance. Two authors evaluated lymphopenia as a predictive factor for toxicity. Ray Coquard *et al* conducted two studies

(54,55) showing that lymphocyte count at day one of chemotherapy < 0.7 G/L was an independent prognostic factor for early death after chemotherapy and for FN, in large cohort of patients (including BC patients). Choi *et al* (56), in contrary couldn't establish a relation between day one lymphopenia and FN in a cohort of patients (including 13% of BC patients) receiving their first course of chemotherapy.

Another limitation of our work is our inability to robustly evaluate if IBM could be predictive for non-hematological toxicities, due to a small number of these events in our retrospective series. Dedicated studies on cardiac, neurological, or hepatic toxicities remains necessary to draw conclusion regarding possible associations between IBM and these toxicities.

NLR has also been studied in other cancers, and more specifically in patients receiving NACT. Chen *et al* (57) found a relation between NLR and DFS / OS in univariate but not in multivariate analysis in 91 patients receiving NACT for stomach cancer. Shen *et al* (58) did not find any correlation between NLR and survival in 202 patients receiving neoadjuvant chemo-radiotherapy for locally advanced rectal cancer. Buisan *et al* (59) found that NLR was prognostic for survival in 50 patients with squamous-cells features bladder cancer receiving NACT. Li *et al* (13) published a large meta-analysis on 6243 patients affected by different kind of cancer (including 1 507 BC) receiving NACT. He showed that high NLR was associated with a lower PCR rate, low NLR was associated with better OS, cancer specific survival, DFS and recurrent free survival. Whether the discrepancies between our work and this meta-analysis are linked to statistical power or heterogeneity of the prognostic value of NLR between tumor types need to be further evaluated.

In conclusion, IBM are an easy and efficient tool to evaluate patient's prognostic and the risk of FN. Additional studies evaluating larger populations, as well dedicated prospective studies, are needed in order to evaluate if IBM could also be reliably predictive for PCR.

Table 1: Patients characteristics

Characteristics	No (%)
Age (median)	50.3 (25.3-76.6)
Menopausal status	
Yes	103 (36.8)
No	177 (63.2)
T stage (before NACT)	
T0	2 (0.7)
T1	22 (7.9)
T2	165 (58.9)
T3	47 (16.8)
T4	43 (15.4)
Missing	1 (0.3)
Node status (before NACT)	
N-	129 (46.1)
N+	145 (51.8)
Missing	6 (2.1)
Inflammatory BC	
Yes	39 (14.2)
No	241 (85.8)
Histology	
Ductal	235 (84)
Lobular	27 (9.6)
Other	18 (6.4)
Histological grade	
1	5 (1.8)
2	123 (43.9)
3	146 (52.2)
Missing	6 (2.1)
Differentiation (N=215)	
1	1 (0.5)
2	21 (9.8)
3	193 (89.7)
Nucleus (N=216)	
1	3 (1.4)
2	77 (35.6)
3	136 (63)
Mitosis (N=216)	
1	70 (32.4)
2	70 (32.4)
3	76 (35.2)
Her2 status	
Positive	81 (28.9)
Negative	199 (71.1)
HR status	
Positive	168 (60)
Negative	112 (40)
Molecular subtype	
HR+/Her2-	127 (45.4)
HR+/Her2+	41 (14.6)
HR-/Her2+	40 (14.3)
HR-/Her2-	72 (25.7)
Baseline biology : median (range)	
Hemoglobin (g/dl)	13.6 (8.0-15.4)
Platelets (G/L)	264 (124-452)
White blood cell count (G/L)	6.8 (1.5-30)
Lymphocyte count (G/L)	1.9 (0.6-26)
PNN (G/L)	3.9 (1.4-11.6)
NLR	2.0 (0.1-17.3)
PLR	132.3 (6.9-514.9)

NACT: neo adjuvant chemotherapy, BC: breast cancer, HR: hormone receptor, PNN: neutrophils, NLR: neutrophil to lymphocyte ratio, PLR: neutrophil to lymphocyte ratio

Table 2: Univariate and multivariate logistic regression of predictive factors for pathological complete response (PCR)

PCR	Univariate				Multivariate	
Variable	**No**	**Yes**	**Total**	***p***	**Odd Ratio (95%CI)**	***p***
Age (year) • < 50.25 • ≥ 50.25	 99 (48.1%) 107 (51.9%)	 41 (55.4%) 33 (44.6%)	 140 (50%) 140 (50%)	0.278		
cT • T 0/2 • T 3/4	 140 (68.0%) 66 (32.0%)	 49 (67.1%) 24 (32.9%)	 189 (67.7%) 90 (32.3%)	0.895		
cN • Negative • Positive	 88 (44.0%) 112 (56.0%)	 41 (55.4%) 33 (44.6%)	 129 (47.1%) 145 (52.9%)	0.093	 1 0.43 (0.23-0.82)	 0.010
Inflammatory BC • No • Yes	 174 (85.7%) 29 (14.3%)	 61 (85.9%) 10 (14.1%)	 235 (85.8%) 39 (14.2%)	0.967		
Histological grade • 1 • 2 • 3	 106 (52.5%) 96 (96 (47.5%)	 22 (30.6%) 50 (69.4%)	 128 (46.7%) 146 (53.3)	0.001	 1 0.13 (0.07-0.27) 0.28 (0.12-0.63)	 <0.001 0.002
Histologic type • Ductal • Lobular • Others	 168 (81.5%) 23 (11.2%) 15 (7.3)	 67 (90.5%) 4 (5.4%) 3 (4.1%)	 235 (83.9%) 27 (9.7%) 18 (6.4%)	0.233		
Hormone receptor • Negative • Positive	 65 (31.6%) 141 (68.4%)	 47 (63.5%) 27 (36.5%)	 112 (40.0%) 168 (60.0%)	<0.001		
Molecular subtype • HR+ Her2 - • HR+ Her2 + • HR – Her2 + • HR – Her2 -	 116 (56.3%) 25 (12.1%) 18 (8.8%) 47 (22.8%)	 11 (14.9%) 16 (21.6%) 22 (29.7%) 25 (33.8%)	 127 (45.4%) 41 (14.6%) 40 (14.3%) 72 (25.7%)	<0.001	 1 7.98 (3.13-20.34) 11.94 (4.76-29.91) 4.65 (1.98-10.89)	 <0.001 <0.001 <0.001
Platelet count • < 264 G/L • ≥ 264 G/L	 97 (47.1%) 109 (52.9%)	 44 (59.5%) 30 (40.5%)	 141 (50.4%) 139 (49.6%)	0.068		
White blood cell count • < 6.75 G/L • ≥ 6.75 G/L	 96 (46.6%) 110 (53.4%)	 44 (59.5%) 30 (40.5%)	 140 (50.0%) 140 (50.0%)	0.058		
Neutrophil count • < 1.5 G/L • ≥ 1.5 G/L	 1 (0.5%) 205 (99.5%)	 0 (0.0%) 74 (100.0%)	 1 (0.4%) 279 (99.6%)	1.000		
Lymphocyte count • < 1 G/L • ≥ 1 G/L	 7 (3.4%) 199 (96.6%)	 1 (1.4%) 73 (98.6%)	 8 (2.9%) 272 (97.1%)	0.685		
NLR • < 2 • ≥ 2	 103 (50.0%) 103 (50.0%)	 34 (45.9%) 40 (54.1%)	 137 (48.9%) 143 (51.1%)	0.550		
PLR • < 150 • ≥ 150	 132 (64.1%) 74 (35.9%)	 45 (60.8%) 29 (39.2%)	 177 (63.2%) 103 (36.8%)	0.617		

BC: breast cancer, cT: clinical tumor size, cN: clinical node involvement, HR: hormone receptor, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio

Table 3: Univariate and multivariate logistic regression of prognostic factors for recurrence free survival (RFS)

RFS	Univariate		Multivariate	
Variable	**Hazard Ratio (95%CI)**	***p***	**Hazard Ratio (95%CI)**	***p***
Age (year)				
• < 50.25	1			
• ≥ 50.25	1.50 (0.91-2.46)	0.111		
cT				
• T 0/2	1		1	
• T 3/4	2.01 (1.23-3.26)	0.005	2.07 (1.26-3.39)	0.004
cN				
• Negative	1			
• Positive	1.61 (0.97-2.69)	0.066		
Inflammatory BC				
• No	1			
• Yes	2.34 (1.33-4.12)	0.003		
Histological grade				
• 1/2	1		1	
• 3	1.12 (0.68-1.84)	0.657	0.84 (0.47-1.51)	0.65
Histologic type				
• Ductal	1			
• Lobular	0.93 (0.40-2.16)	0.866		
• Others	1.84 (0.84-4.06)	0.129		
HR				
• Negative	1			
• Positive	0.48 (0.29-0.78)	0.003		
Molecular subtype				
• HR+ Her2 -	1		1	
• HR+ Her2 +	1.135 (0.505-2.551)	0.759	1.55 (0.73-3.33)	0.253
• HR – Her2 +	1.378 (0.634-2.993)	0.418	1.89 (0.86-4.14)	0.111
• HR – Her2 -	2.669 (1.511-4.714)	0.001	4.11 (2.28-7.42)	<0.001
PCR				
• No	1		1	
• Yes	0.37 (0.18-0.78)	0.009	0.27 (0.12-0.56)	0.001
Platelet count				
• < 264 G/L	1			
• ≥ 264 G/L	1.73 (1.05-2.84)	0.031		
White blood cell count	1			
• < 6.75 G/L	1.14 (0.70-1.86)	0.593		
• ≥ 6.75 G/L				
Neutrophil count				
• < 1.5 G/L	1		1	
• ≥ 1.5 G/L	0.06 (0.01-0.48)	0.007	0.06 (0.03-0,12)	< 0.001
Lymphocyte count				
• < 1 G/L	1			
• ≥ 1 G/L	0.89 (0.22-3.64)	0.871		
NLR				
• < 2	1			
• ≥ 2	1.02 (0.63-1.66)	0.930		
PLR				
• < 150	1		1	
• ≥ 150	1.65 (1.01-2.69)	0.044	1.91 (1.15-3.16)	0.012

cT: clinical tumor size, cN: clinical node involvement, BC: breast cancer, HR: hormone receptor, PCR: pathological complete response, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio

Table 4: Univariate and multivariate logistic regression of prognostic factors for overall survival (OS)

OS	Univariate		Multivariate	
Variable	**Hazard Ratio (95%CI)**	***p***	**Hazard Ratio (IC95%CI)**	***p***
Age (year)				
• < 50.25	1			
• ≥ 50.25	1.60 (0.91-2.83)	0.103		
cT				
• T 0/2	1		1	
• T 3/4	2.15 (1.24-3.73)	0.006	2.43 (1.37-4.30)	0.002
cN				
• Negative	1			
• Positive	1.42 (0.80-2.51)	0.232		
Inflammatory BC				
• No	1			
• Yes	2.21 (1.17-4.16)	0.014		
Histological grade				
• 1/2	1			
• 3	1.00 (0.57-1.76)	0.993		
Histologic type				
• Ductal	1			
• Lobular	0.76 (0.27-2.12)	0.604		
• Others	1.20 (0.43-3.33)	0.732		
HR				
• Negative	1			
• Positive	0.37 (0.21-0.65)	0.001		
Molecular subtype				
• HR+ Her2 -	1		1	
• HR+ Her2 +	1.33 (0.15-3.47)	0.555	1.77 (0.72-4.34)	0.211
• HR – Her2 +	1.15 (0.41-3.20)	0.785	1.44 (0.50-4.13)	0.501
• HR – Her2 -	4.15 (2.16-7.96)	<0.001	6.59 (3.34-13.01)	<0.001
PCR				
• No	1		1	
• Yes	0.43 (0.20-0.97)	0.041	0.29 (0.13-0.66)	0.003
Platelet count				
• < 264 G/L	1			
• ≥ 264 G/L	1.76 (1.00-3.09)	0.049		
White blood cell count				
• < 6.75 G/L	1			
• ≥ 6.75 G/L	1.39 (0.80-2.41)	0.248		
Neutrophil count				
• < 1.5 G/L	1		1	
• ≥ 1.5 G/L	0.16 (0.02-1.17)	0.071	0.12 (0.06-0.24)	<0.001
Lymphocyte count				
• < 1 G/L	1			
• ≥ 1 G/L	0.70 (0.71-2.89)	0.624		
NLR				
• < 2	1			
• ≥ 2	0.96 (0.55-1.66)	0.890		
PLR				
• < 150	1		1	
• ≥ 150	1.49 (0.85-2.60)	0.160	1.83 (1.03-3.24)	0.039

cT: clinical tumor size, cN: clinical node involvement, BC: breast cancer, HR: hormone receptor, PCR: pathological complete response, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio

Table 5 : multivariate logistic regression of predictive factors for febrile neutropenia

Febrile Neutropenia	Univariate				Multivariate	
Variable	**No**	**Yes**	**Total**	***p***	**Odd Ratio (95%CI)**	***p***
Age (year) • < 50.25 • ≥ 50.25	 124 (52.3%) 113 (47.7%)	 16 (37.2%) 27 (62.8%)	 140 (50.0%) 140 (50.0%)	0.068		
cT • T 0/2 • T 3/4	 156 (66.1%) 80 (33.9%)	 33 (76.7%) 10 (23.3%)	 189 (67.7%) 90 (32.3%)	0.170	 1 0.43 (0.20-0.91)	 0.028
cN • Negative • Positive	 107 (46.3%) 124 (53.7%)	 22 (21.2%) 21 (48.8%)	 129 (47.1%) 145 (52.9%)	0.559		
Inflammatory BC • No • Yes	 200 (85.8%) 33 (14.2%)	 35 (85.4%) 6 (14.6%)	 235 (85.8%) 39 (14.2%)	0.936		
Histological grade • 1 • 2 • 3	 112 (48.3%) 120 (51.7%)	 16 (38.1%) 26 (61.9%)	 128 (46.7%) 146 (53.3%)	0.228		
Histologic type • Ductal • Lobular • Others	 198 (82.5%) 23 (9.6%) 16 (7.9%)	 37 (86.0%) 4 (9.3%) 2 (4.7%)	 235 (83.9%) 27 (9.6%) 18 (6.5%)	1.000		
HR • Negative • Positive	 86 (36.3%) 151 (63.7%)	 26 (60.5%) 17 (39.5%)	 112 (40.0%) 168 (60.0%)	0.003		
Molecular subtype • RH+ Her2 - • RH+ Her2 + • RH – Her2 + • RH – Her2 -	 112 (47.3%) 39 (16.5%) 28 (11.7%) 58 (24.5%)	 15 (34.5%) 2 (4.8%) 12 (27.9%) 14 (32.8%)	 127 (45.5%) 41 (14.6%) 40 (14.3%) 72 (25.6%)	0.007	 1 0.21 (0.05-0.93) 2.18 (0.93-5.11) 1.09 (0.51-2.34)	 0.039 0.072 0.826
Platelet count • < 264 G/L • ≥ 264 G/L	 112 (47.3%) 125 (52.7%)	 29 (67.4%) 14 (32.6%)	 141 (50.4%) 139 (49.6%)	0.014	 1 0.40 (0.21-0.75)	 0.004
White blood cell count • < 6.75 G/L • ≥ 6.75 G/L	 109 (46.0%) 128 (54.0%)	 31 (72.1%) 12 (27.9%)	 140 (50.0%) 140 (50.0%)	0.002	 1 0.35 (0.17-0.72)	 0.004
Neutrophil count • < 1.5 G/L • ≥ 1.5 G/L	 0 (0.0%) 237 (100.0%)	 1 (2.3%) 42 (97.7%)	 1 (0.4%) 279 (99.6%)	0.154		
Lymphocyte count • < 1 G/L • ≥ 1 G/L	 7 (3.0%) 230 (97.0%)	 1 (2.3%) 42 (97.7%)	 8 (2.9%) 272 (97.1%)	1.000		
NLR • < 2 • ≥ 2	 106 (44.7%) 131 (55.3%)	 31 (72.1%) 12 (27.9%)	 137 (48.9%) 143 (51.1%)	0.001	 1 0.28 (0.13-0.58)	 0.001
PLR • < 150 • ≥ 150	 148 (62.4%) 89 (37.6%)	 29 (67.4%) 14 (32.6%)	 177 (63.2%) 103 (36.8%)	0.532		

cT: clinical tumor size, cN: clinical node involvement, BC: breast cancer, HR: hormone receptor, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio

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Article 2

Neutrophil to lymphocyte ratio as prognostic and predictive factor in breast cancer patients: a systematic review

Evaluation du ratio neutrophiles sur lymphocytes comme facteur pronostique et prédictif dans le cancer du sein : revue de la littérature.

Iléana CORBEAU, William JACOT, Séverine GUIU

ABSTRACT

Inflammatory blood markers (IBM), such as neutrophil to lymphocyte ratio (NLR), have emerged as potential prognostic factors in various cancers, including breast cancer (BC), potentially allowing an easy, minimally invasive, evaluation of a given cancer's prognosis and treatment outcome. We report here a systematic overview of published data evaluating NLR as prognostic factor or predictive factor for pathological complete response (PCR) and toxicity in early and advanced BC. A total of 45 articles were identified. NLR was found to be an independent prognostic factor for survival in most of the adjuvant treatment studies. However, no significant correlation was found between survival and NLR for early BC patients receiving neo-adjuvant chemotherapy (NACT) and advanced BC patients. Most studies failed to find a significant correlation between NLR and PCR after NACT. Finally, some data showed that IBM could be predictive of chemotherapy-related toxicity.

Keywords: breast cancer, inflammatory blood markers, neutrophil to lymphocyte ratio, prognostic factor, predictive factor, pathological complete response, toxicity

1. INTRODUCTION

Breast cancer (BC) is a heterogeneous disease, its prognosis depending on the tumor stage (localized disease *versus* metastatic disease) and the molecular subtype. Today's management of BC includes multidisciplinary and multimodal treatments such as surgery, radiation therapy, chemotherapy (CT), endocrine therapy and / or targeted therapies (1,2). Some predictive and / or prognostic factors are well known (for example hormone receptor status, Her2 overexpression / amplification, histological grade or stage). However, there is a persistent need for more predictive and prognostic factors in order to adapt as precisely as possible each patients' treatment.

Over the past few years, inflammatory blood markers (IBM) have emerged as predictive and prognostic factors, and especially the neutrophil to lymphocyte ratio (NLR) defined as the ratio of absolute neutrophil count to absolute lymphocyte count. Lymphopenia and high NLR before CT initiation have been inconsistently reported to be associated with worse response to neoadjuvant chemotherapy (NACT) and to poor prognosis in different cancer types, including BC (3,4).

The role of inflammation on cancer is now well established (5) and has been described at the different stages of cancer development (initiation, promotion, invasion and metastasis). Activated inflammation cells serve as sources of Reactive Oxygen Species (ROS) and Reactive Nitrogen intermediate (RNI) that can induce DNA damage and genome instability therefore initiating cancer (6,7) or interfering with DNA repair systems (8). Inflammation enhances the production of growth factors and cytokines that can confer a stem-cell like phenotype upon tumor progenitors; it also involves the angiogenetic switch which favors tumor progression. Neutrophils in particular have more and more been studied and there is now evidences that neutrophils can promote tumor growth and play a role in metastasis development (9,10). Their ability to secrete proteases, and particularly matrix metalloproteases (MMP) helps them promoting tumor invasion. They are also involved in tumor progression through their capacity to activate signal transducer and activators of transcription 3 (STAT3) and through their capacity to promote neo-angiogenesis (11).

Tumor infiltrating lymphocytes (TILs) have been widely studied in recent years, especially in BC (12). It has been shown that TILs, and more particularly lymphocytes belonging to the

innate arm of the immune system, were likely to recognize and eliminate malignant cells. Therefore, they play a central role and low TILs could be predictive for fewer responses to NACT (13) and associated to poor prognosis (14,15).

Peripheral IBM could be helpful for predicting both patients' prognosis and the response to NACT in BC. Many studies have evaluated NLR, with conflicting results regarding its ability to be a predictive and / or a prognostic factor (11,16–21). Total white blood cell count, neutrophil count, lymphocyte count or other ratios such as platelet to lymphocyte ratio (PLR) have also been studied with the same conflicting results.

Here we systematically collected published data evaluating the predictive or prognostic role of NLR in BC patients. We will first summarize the published data on NLR and treatment efficacy regarding survival (disease free survival [DFS], breast cancer specific survival [BCSS] and overall survival [OS)] in patients with early BC (receiving NACT or adjuvant treatment) and in patients with advanced BC. We will also summarize data on the predictive value of NLR for pathological complete response (PCR).
The second part of our work will evaluate the correlation between CT-related toxicity and NLR and / or lymphopenia.

2. MATERIAL AND METHODS

2.1 Search strategy

A systematic search on PubMed database was performed, using search terms of "neutrophil to lymphocytes ratio" AND "breast cancer" or "lymphopenia" AND "breast cancer". We also looked for papers corresponding to the search for "toxicity" AND "neutrophil to lymphocyte ratio" OR "lymphopenia" AND "breast cancer". Literature reviewing was updated on February 2019. Citation lists from article of interest found on PubMed were screened in order to ensure exhaustivity of the papers included in our work.

2.2 Study Selection (Figure 1)

For the first part of our work focusing on treatment efficacy, all articles with only BC cohort, PCR and / or survival analysis as primary objectives were included. Papers mixing different situations (neoadjuvant, adjuvant and metastatic settings) were excluded. For the second part focusing on toxicity, all articles reporting data about BC, IBM and CT-related toxicity were included. We excluded papers that were in another language than English.

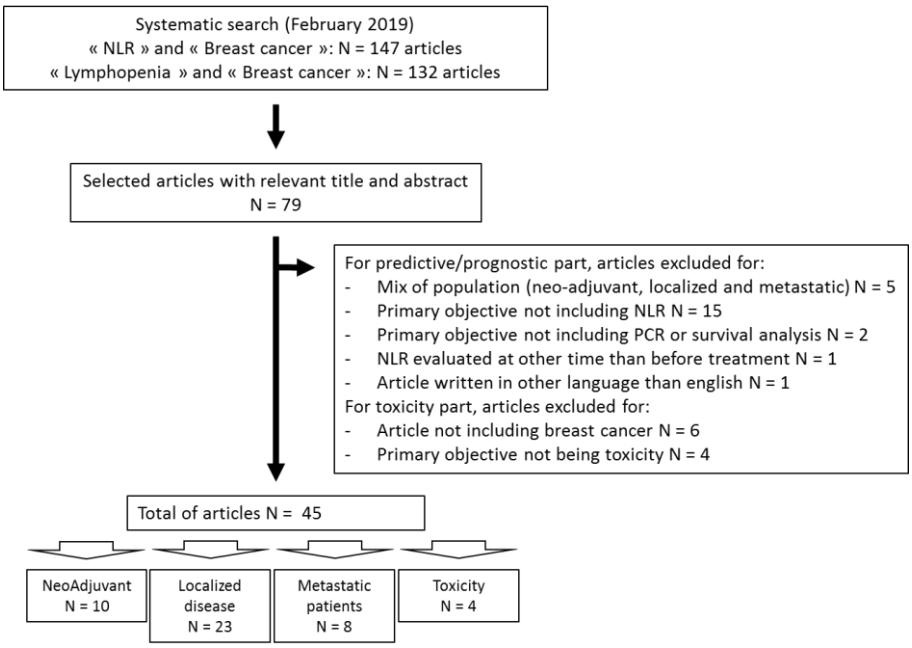

Figure 1 Flow chart of the study selection

2.3 Data extraction

The following information were extracted from each study: name of first author and year of publication, population of interest, description of endpoints based on BC molecular subtypes, number of patients enrolled, ethnicity, treatment received, chosen cut-off for NLR, primary objective, results on primary objectives (univariate analysis), results on subgroup analysis (if applicable), secondary objectives and their results, existence of a multivariate model on NLR results and if so, results on multivariate model and adjustment covariates. We distinguished three populations: patients receiving NACT, patients receiving adjuvant treatment, and

patients with advanced BC. For toxicity, we selected articles that studied CT-related toxicity according to lymphocyte count or NLR. Data on population of interest, treatment received and toxicity were reported.

In cases of selected articles reporting data on other IBM (such as lymphocyte count or PLR) as predictive and / or prognostic factors, the data were included in our tables.

2.4 Definitions

DFS was defined as the time between the diagnosis (or the date of surgery for patients receiving adjuvant CT) and the date of relapse (local recurrence or metastases to distant sites) and / or death from any cause, whichever comes first, for some papers. Some papers used recurrence free survival (RFS) as primary objective. RFS had the same definition than DFS, therefore we used the term of DFS for DFS or RFS in this work.

BCSS was calculated from the date of diagnosis until the date the patient succumbed to the disease or last follow up time. Some papers reported data on disease specific survival (DSS) which had the same definition than BCSS, therefore we used the term of BCSS for BCSS or for DSS in this work.

OS was defined, for all studies, as the time between the date of diagnosis (or the first day of surgery) and the date of death due to any reason (and / or the date of last follow up for some papers).

Finally, progression-free survival (PFS) was defined as the time from treatment initiation to the date of disease progression or death from any cause.

3. RESULTS

3.1 Efficacy

3.1.1 In early BC

3.1.1.1 Patients receiving NACT (Table 1)

Ten studies reported data on NLR as predictive or prognostic factor in patients receiving NACT (22–31). Out of those 10 studies, 8 included patients with all molecular subtypes (22–29), one included only patients with triple negative breast cancer (TNBC) subtype (31) and another studied only patients with hormone

receptor positive / HER2-negative BC (30). The NLR cut off for statistical analyses was between 1.7 and 3.33 and was obtained by performing receiver operating characteristic (ROC) curves analysis for each study. Number of patients enrolled in studies was between 78 and 373. Half of the studies reported data on Asian population (23,25,28,30,31). In 9 studies NACT protocols was reported and was based on anthracycline and / or taxane regimens (23–31).

3.1.1.1.1 Results on PCR

3.1.1.1.1.1 Studies including all molecular subtypes

Seven studies had PCR rate according to NLR as primary objective (22–25,27–29). For all studies (except for two with no definition reported), PCR was defined as complete disappearance of invasive tumour both in the breast and in the lymph nodes (patients with residual ductal carcinoma *in situ* were also considered to have achieved PCR: ypT0/is pN0). Out of those 7 studies, only 3 (43%) reported a significant correlation between NLR and PCR in univariate analysis (23,25,28). Only one study, from Qian *et al*, reported data with multivariate analysis and found that NLR was not an independent prognostic factor for PCR (p = 0.254) (28).

3.1.1.1.1.2 Studies including only specific molecular subtypes

Chae *et al* studied 87 cases of TNBC and showed a relation between NLR and PCR in univariate and multivariate model (odds ratio [OR] = 4.274; 95%CI 1.451-12.658; p = 0.008) (31).

3.1.1.1.1.3 Subgroup analyses

Suppan *et al* (24) compared patients that received both anthracyclines and taxanes and patients that received anthracyclines or taxanes. They didn't show any correlation between NLR and PCR in any of the two groups. They also compared the different molecular subtypes and did not identify a specific subgroup for which there would be a correlation between NLR and PCR.

Graziano *et al* (27) showed that patients with NLR^{low} / PLR^{low} had higher PCR rates than patients with NLR^{high} / PLR^{high} (OR = 1.98; 95%CI 1.01-3.89; p = 0.044).

3.1.1.1.2 Results on DFS

3.1.1.1.2.1 Studies including all molecular subtypes

DFS was a primary objective in 6 studies (23–26,28,29). Out of them, only two (33%) reported that higher NLR was correlated to shorter DFS in univariate analysis (25,26). Three studies (50%) reported data on NLR and DFS with multivariate analyses (24–26): only one of them (33%), written by Chen *et al* (25), found that NLR was an independent prognostic factor (HR = 1.57; 95%CI 1.05-3.57; $p < 0.05$).

3.1.1.1.2.2 Studies including only specific molecular subtypes

Koh *et al* (30), that were interested in patients with hormone receptor positive / Her2 negative BC, reported that NLR was an independent prognostic factor for DFS in this population (HR = 3.87; 95%CI 1.64-9.14; p = 0.002).

2.1.1.1.2.3 Sub group analyses

Asano *et al* (23) showed that in their sub-group of 61 patients with TNBC, NLR was correlated to DFS in univariate analysis but was not an independent prognostic factor for DFS.

3.1.1.1.3 Results on OS and BCSS

3.1.1.1.3.1 Studies including all molecular subtypes

Four studies had data on NLR and OS with univariate analysis (23,26,28,29). Out of them only one (25%), written by Marin-Hernandez *et al* (26), showed a significant association between NLR and OS in univariate analysis but NLR was not found to be an independent prognostic factor for OS (p = 0.543).

Chen *et al* (25) reported data on BCSS and showed that NLR is an independent prognostic factor for BCSS (HR = 2.21; 95%CI 1.01-4.39; $p < 0.05$) in their population of 215 stages II and III BC.

3.1.1.1.3.2 Studies including only specific molecular subtypes

Koh *et al* (30) studied NLR as prognostic factor for OS in 157 patients with hormone receptor positive / Her2 negative BC and found it was an independent prognostic factor (HR = 24.87; 95%CI 3.1-201.3; $p = 0.003$).

3.1.1.1.3.3 Sub group analyses

Koh *et al* (30) also showed that correlation between NLR and OS was even stronger in patients with stage III BC compared to patients with stage II BC.

3.1.1.1.4 Conclusion on NLR as prognosis and predictive factor in patients receiving NACT

Six papers reported data with multivariate analyses on patients receiving NACT (24–26,28,30,31). One out of two analyses (50%) found a correlation between NLR and PCR (31), two out four analyses (50%) found a correlation between NLR and DFS (25,30), two out of four analyses (50%) found a correlation between NLR and OS (30,31) and finally the only analysis on NLR and BCSS found a significant correlation (25) . These 9 analyses included a total of 1 558 patients. Precaution should be taken on conclusions since out of the 6 studies, two studied only one specific molecular subtype (TNBC or hormone receptor positive / Her2 negative patients). Table 2 summarizes the multivariate analyses and adjustment factors.

Table 1: Articles including data on NLR as predictive and prognostic factor in patients receiving NACT

First author	Number of patients	Treatment received	Primary objective	Cut off	Results on primary objective (univariate analysis)	Results on multivariate model
Erylimaz 2014	**78 patients including** all molecular subtypes	NS	NLR predictive for PCR	2.33	- NLR and PCR	
Asano 2016	**177 patients** including 116 non TNBC (65.5%) 61 TNBC (34.5%)	Anthracyclines + taxanes	NLR predicitive and prognostic	3 (chosen before statistical analysis)	- NLR and DFS (p = 0.849) - NLR and OS (p = 0.965) PCR was achieved in 28.6% with high NLR *vs* 56.9 patients with low NLR (p < 0.001)	
Suppan 2015	**247 patients** including 150 ER+ (60.7%) 134 PR+ (54.3%) 49 Her2 positive (19.8%)	Anthracyclines +Taxanes (58.3%); Anthracylcines (38.2%); Taxanes (2.8%); other (6.1%)	NLR predicitive and prognostic	comparison of median NLR	- NLR and DFS (p = 0.363) - NLR and PCR (OR = 1.081; p = 0.053)	- NLR and DFS (HR = 1.01; p = 0.738)
Chen 2016	**215 patients** including 120 luminal A (55.8%) 52 luminal B (24.2%) 25 Her2 positive (11.6%) 18 TNBC (8.4%)	Anthracyclines + taxanes (74.9%); anthracyclines (19.1%); taxanes (6%)	NLR predicitive and prognostic	2.1	NLR^{low} group showed higher PCR rate vs NLR^{high} group (24.5% *vs* 14.3%; p < 0.05) + NLR and DFS (H = 2.11; p < 0.05) + NLR and BCSS (HR = 2.45; p < 0.05)	+ NLR and DFS (HR = 1.57; p < 0.05) + NLR and BCSS (HR = 2.21; p < 0.05)
Marin-Hernandez 2017	**150 patients** including 32 luminal A (21.3%) 44 luminal B (29.4%) 35 Her2 positive (23.3%) 39 TNBC (26%)	Anthracyclines + taxanes for all patients (except for 3 that recieved everolimus in the context of a clinical trial)	blood parameters as prognostic	3.33	+ NLR and DFS (OR = 0.39; p = 0.019) + NLR and OS (OR = 0.38; p = 0.030)	- NLR and DFS (p = 0.154) - NLR and OS (p = 0.543)
Graziano 2019	**373 patients** including 132 luminal A (35.4%) 44 luminal B/Her2 neg (11.8%) 69 luminal B/Her2 pos (18.5%) 62 TNBC (16.6%) 66 Her2 positive (17.7%)	Anthracyclines + taxanes (56.8%); others received anthracyclines or taxanes as single agent or combination	NLR predictive of PCR	2.42	- NLR and PCR (OR = 1.53; p = 0.125) - PLR and PCR (OR = 1.59; p = 0.084)	
Qian 2018	**180 patients for PCR** including 24 luminal A (13.3%) 60 luminal B (33.3%) 18 Her2 positive (10%) 40 TNBC (22.2%) 38 not available (21.2%) **131 patients for survival**	Taxane and/or anthracyline based chemotherapy Only 40% of Her2 positive cancer where treated with trastuzumab	NLR/PLR predictive and prognostic	2.44	+ NLR and PCR (20% *vs* 7.8%; p = 0.030) survival analysis on 131 patients: - NLR and DFS (p = 0.535) or OS (data not available)	- NLR and PCR (p = 0.254)

Table 1 (continued)

First author	Number of patients	Treatment received	Primary objective	Cut off	Results on primary objective (univariate analysis)	Results on multivariate model
Losada 2018	**104 elderly patients** (>65y) including 23 luminal A (20.4%) 57 luminal B (50.4%) 8 Her2 positive (7.1%) 25 TNBC (22.1%)	Anthracycline, taxanes or both (no more data)	NLR survival and PCR	3.33	- NLR and DFS (p = 0.42) or OS (p = 0.38) - NLR and PCR (p = 0.43)	
Koh 2014	**157 patients** with ER/PR+ and Her2-negative BC	Anthracyclines + taxanes (75.2%); anthracyclines (24.8%)	NLR prognostic	2.25	+ NLR and DFS (HR = 4.01; p = 0.001) + NLR and OS (HR=24.64; p = 0.003)	+ NLR and DFS (HR = 3.87; p = 0.002) + NLR and OS (HR = 24.87; p = 0.003)
Chae 2018	**87 TNBC**	Anthracyclines + taxanes (71.3%), Anthracyclines (28.7%)	NLR predictive of PCR	1.7	low NLR had higher PCR rate (42.1% *vs* 18.4%; p = 0.018)	+ NLR and PCR (OR = 4.27; p = 0.008)

NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, PCR: pathological complete response, DFS: disease free survival, OS: overall survival, NACT: neo adjuvant chemotherapy, ER: estrogen receptor, PR: progesterone receptor, BCSS: breast cancer specific survival, OR: odd ratio, HR: hazard ratio, BC: breast cancer

Table 2: Multivariate models (results and adjustment factors) for patients treated with NACT

All molecular subtypes					
	PCR	DFS	OS	BCSS	Total
Number of multivariate models	1	3	1	1	6
Number of unique patients	180	612	150	215	1157
NLR significantly associated with n (%)	0 (0%)	1 (33%)	0 (0%)	1 (100%)	2 (33%)
Adjustment factors (%)					
Hormone receptors	100	67	NI	100	
T	NI	100	100	100	
N	NI	67	NI	100	
Age	NI	33	100	NI	
Histological Grade	NI	33	NI	100	
Molecular subtype	100	NI	NI	NI	
Ki67	100	NI	NI	NI	
CRP	NI	33	NI	100	
Operation method	NI	33	NI	100	
Lymphocyte count	100	33	100	NI	
Monocyte count	NI	33	100	NI	
Neutrophil count	NI	33	100	NI	
LMR	NI	33	100	NI	
NMR	NI	33	100	NI	
TNBC					
	PCR				Total
Number of multivariate models	1				1
Number of unique patients	87				87
NLR significantly associated with n (%)	1 (100%)				1 (100%)
Adjustment factors (%)					
Histological subtype	100				
Histological grade	100				
Ki67	100				
ER+ Her2 negative					
		DFS	OS		Total
Number of multivariate models		1	1		2
Number of unique patients		157	157		157
NLR significantly associated with n (%)		1 (100%)	1 (100%)		2 (100%)
Adjustment factors (%)					
PCR		100	100		
All studies					
	PCR	DFS	OS	BCSS	Total
Number of multivariate models	2	4	2	1	9
Number of unique patients	267	769	307	215	1558
NLR significantly associated with n (%)	1 (50%)	2 (50%)	1 (50%)	1 (100%)	5 (55.5%)

NACT: neo adjuvant chemotherapy, PCR: pathological complete response, DFS: disease free survival, OS: overall survival, BCSS: breast cancer specific survival, NLR: neutrophil to lymphocyte ratio, LMR: lymphocyte to monocyte ratio, NMR: neutrophil to monocyte ratio, NI: not indicated

3.1.1.1.5 Results on other IBM

Out of these studies, 4 (26–29) were also interested in total lymphocyte count (2 studies) (26,28) or total neutrophil count before treatment (2 studies) (26,28) and other ratios such as lymphocyte to monocyte ratio (LMR) (2 studies) (26,29), neutrophil to monocyte ratio (NMR) (2 studies) (26,29) and PLR (2 studies) (27,29) as predictive and prognostic factors. Lymphocyte count was not correlated to DFS nor OS in Marin Hernandez *et al*'s study (26) but was an independent predictive factor for PCR in multivariate analysis in Qian *et al*'s study (OR = 4.37; 95%CI 1.43-13.39; *p*=0.01) (28). Neutrophil count was not correlated to PCR in Qian *et al'*s study (28), was not correlated to OS either in Marin Heranandez *et al*'s study (26), but was an independent prognosis factor in multivariate analysis for DFS in Qian *et al*'s study (28). PLR was not correlated to PCR in Graniano *et al*'s study (27) nor to DFS or OS in Lasada *et al's* study (29) (univariate analysis). Marin Hernandez *et al* (26) found no correlation between NMR, LMR and survival (DFS and OS) in univariate and multivariate analysis. These results are consistent with Losada *et al* that found no correlation between LMR nor NMR and DFS or OS (29).

3.1.1.2 Patients receiving adjuvant treatment (Table 3)

Twenty-three studies reported data on NLR as prognostic factor in patients with localized BC receiving adjuvant treatment (32–53). Out of those 23 studies, 18 (78%) included patients with all molecular subtypes (32–48), while 4 studied only TNBC (49–52), and one studied hormone receptor negative cancer (whatever the Her2 status) (53). The NLR cut off for statistical analyses, obtained by performing ROC curves analysis for most of the studies (78%), was set between 1.34 and 4. Number of patients enrolled in the individual studies varied from 90 to 1570 patients. Fifteen studies (65%) reported data on Asian population (32,35,36,38,39,42–44,46–49,51,53). Adjuvant CT regimens were reported in only 6 studies, consisting on anthracyclines and / or taxanes-based regimens (33,38,43,45,48,51).

Table 3: Articles including data on NLR as prognosis factor in patients receiving adjuvant treatment

Author	Number of patients	Treatment received	Primary objective	Cut off	Results on primary objective (univariate analysis)	Results on multivariate model
Noh 2013	**442 patients** including 177 luminal A (48.7%) 69 luminal B (19.0%) 36 Her2 positive (10.0%) 81 TNBC (22.3)	NS	NLR as prognostic factor for DSS	2.5	+ NLR and DSS 5 year survival: 88.6% *vs* 96.4% ; 10 year survival : 84.3% *vs* 92.2% ; p = 0.009	+ NLR and BCSS (HR = 4.08; p = 0.003)
Cihan 2014	350 patients including 194 ER+ (55.4%) 183 PR+ (52.3%) 110 Her2 positive (31.4)	CT (94.3%) (based on anthracyclines for 71.7%)	NLR as prognostic factor for DFS and OS	NLR : 3 P	- NLR and DFS (0R = 0.8; *p* = 0.410) - NLR and OS (OR = 0.7; *p* = 0.432)	
Forget 2014	**720 patients** including 601 ER+ (83.5%) 573 PR+ (79.6%) 67 Her2 positive (9.3%)	NS	NLR as prognostic factor for DFS and OS	3.3	+ NLR and DFS (HR = 2.20; *p* = 0.004) + NLR and OS (HR = 2.70; *p* = 0.020)	+ NLR and DFS (HR = 1.99; p = 0.010) + NLR and OS (HR = 2.35; p = 0.046)
Nakano 2014	**167 patients** including 130 ER+ (77.8%) 93 PR+ (55.7%) 24 Her2 positive (14.4%)	NS	NLR as prognostic factor for DFS and DSS	2.5 (according to previous studies)	+ NLR and DFS (HR = 2.5; *p* = 0.004) + NLR and BCSS (HR = 3.2; *p* = 0.007)	- NLR and DFS (HR = 2.0; p = 0.070) + NLR and BCSS (HR=2.7; p = 0.045)
Yao 2014	**608 patients** including 330 luminal A (57.9%) 59 luminal B (10.3%) 83 Her2 positive (14.6%) 98 TNBC (17.2%)	NS	NLR as prognostic factor for OS	2.57	- NLR and DFS (*p* = 0.084) + NLR and OS (*p* < 0.001)	+ NLR and OS (RR = 3.63; p = 0.002)
Dirican 2015	**1527 patients** including 1019 ER+ (66.4%) 994 PR+ (64.7%) 249 Her2+++ (16.2%)	adjuvant CT for 83.3% NACT for 9.6%	NLR as prognostic factor for DFS and OS	4	+ NLR and DFS (HR = 2.18; *p* < 0.001) + NLR and OS (HR = 2.82; *p* < 0.001)	+ NLR and DFS (HR = 1.46; p = 0.028) + NLR and OS (HR = 1.91; p = 0.001)
Hong 2016	**487 patients** including 62 luminal A (12.7%) 244 luminal B (50.1%) 59 Her2 positive (12.1%) 94 TNBC (19.3%) 28 NA (5.7%)	adjuvant CT for 73.5% (anthracyclines 30.7%; taxanes 15.6% ; anthracyclines + taxanes 36%; others 17.7%)	NLR as prognostic factor for DFS	1.93	+ NLR and DFS (HR = 2.20; *p* = 0.002) - NLR and 5y-OS (90.8% *vs* 91.7%; *p* = 0.707)	+ NLR and DFS (HR = 1.87; p = 0.011)
Jia 2015	**1570 patients** including 1001 luminal (63.8%) 344 Her2 positive (21.9%) 225 TNBC (14.3%)	adjuvant CT for 85.4%	NLR as prognostic factor for DFS and OS	2.0	+ NLR and DFS (HR = 1.44; *p* = 0.005) + NLR and OS (HR = 1.58; *p* = 0.020)	+ NLR and DFS (HR = 1.50; p = 0.004) + NLR and OS (HR = 1.63; p = 0.022)

Table 3 (continued)

Author	Number of patients	Treatment received	Primary objective	Cut off	Results on primary objective (univariate analysis)	Results on multivariate model
Orditura 2016	**300 patients** including 77 luminal A (25.7%) 124 luminal B Her2 - (41.3%) 51 luminal B Her2 + (17%) 21 Her2 enriched (7%) 27 basal like (9%)	NS	NLR as prognostic factor for DFS	1.97	+ NLR and DFS (HR = 0.45; p = 0.034)	+ NLR and DFS (HR = 2.64; p = 0.013)
Ramos-Esquivel 2017	**172 patients** including 104 ER+ or PR+ and Her2 - (60.5%) 18 ER+ or PR+ and Her2 + (10.5%) 16 ER- and PR- and Her2 + (9.3%) 34 ER- and PR- and Her2 - (19.6%)	Adjuvant CT (83.1%), NACT (22.1%)	NLR as prognostic factor for DFS and OS	3	+ NLR and DFS (HR = 4.20; p < 0.001) + NLR and OS (HR = 4.20; p < 0.001)	- NLR and DFS (HR = 1.97; p = 0.146) - NLR and OS (HR = 1.81; p = 0.192)
Zhang 2016	**162 patients** including 87 ER+ (53.7%) 77 PR+ (47.6%) 37 Her2 positive (22.8%)	NS	NLR as prognostic factor for DFS	1.81 (according to median value)	+ NLR and DFS (HR = 1.81; p = 0.042) - NLR and OS	- NLR and DFS (HR = 1.43; p = 0.223)
Takeuchi 2017	**296 patients** including 253 ER+ (85%) 222 PR+ (75%) 247 Her2 positive (83%)	Adjuvant therapy according to St Gallen recommendations	NLR as prognostic factor for DFS	2.06	- NLR and DFS	
Cho 2018	**661 patients** including 448 luminal (67.8%) 96 Her2 positive (14.5%) 117 TNBC (17.7%)	NS	NLR as prognostic for DFS and DSS	1.34	+ NLR and DFS (RR = 1.18; p < 0.001) + NLR and DSS (RR = 1.27; p < 0.001)	- NLR and DFS (RR = 1.24; p = 0.613) - NLR and BCSS (RR = 1.24; p = 0.681)
Ferroni 2018	**475 patients** including 164 luminal A (35%) 239 luminal B (50%) 15 Her2 positive (3%) 57 TNBC (12%)	NACT for 14.1% adjuvant therapy for 82.5% (with anthracyclines)	NLR as prognostic factor for DFS and OS	2	+ NLR and DFS (HR= 2.28 ; p = 0,001) + NLR and OS (HR = 3.39; p = 0,050)	
Geng 2018	**1374 patients** in testing group including 1038 Hormone receptor + (75.6%) 336 Hormone receptor - (24.4%) 128 Her2 positive (9.3%) 1246 Her2 negative (90.7%) 208 TNBC (15.1%) 1166 No TNBC (84.9%)	96 patients of cohort 1 had NACT	NLR as prognostic factor for DFS	1.878 (in testing group)	+ NLR and DFS testing group (HR = 2.89; p < 0.001)	+ NLR and DFS in testing group (HR = 2.99; p < 0.001)

Table 3 (continued)

Author	Number of patients	Treatment received	Primary objective	Cut off	Results on primary objective (univariate analysis)	Results on multivariate model
Geng 2018	**1084 patients** in validation group 702 Hormone receptor + (64.7%) 382 Hormone receptor - (35.3%) 170 Her2 positive (15.7%) 914 Her2 negative (84.3%) 212 TNBC (19.6%) 872 No TNBC (80.4%)	NS	NLR as prognostic factor for DFS	1.878 (based on testing group)	+ NLR and DFS in validation group (HR = 1.65; *p* = 0.017)	+ NLR and DFS in validation group (HR = 1.64; *p* = 0.023)
Fujimoto 2018	**889 patients** including 699 ER+ (78.6%) 152 Her2 positive (17.1%)	Adjuvant CT for 29.6%	NLR as prognostic factor for DFS	2.72	+ NLR and DFS (HR = 1.56; *p* = 0.047) - NLR and OS (*p* = 0.23)	- NLR and DFS (*p* = 0.14)
Kim 2016	**220 patients** with pN3 BC including 99 Hormone receptor +/Her2 - (45%) 44 Hormone receptor+/Her2 + (20%) 48 Hormone receptor-/Her2 + (21.8%) 29 TNBC (13.2%)	Adjuvant CT (anthracyclines followed by taxanes) for all patients	NLR as prognostic factor for DFS	3 (from previous studies)	+ NLR and 5y-DFS (*p* = 0.043)	+ NLR and DFS (HR = 3.93; p = 0.020)
Qiu 2018	406 TNBC patients	NACT (21.2%) Adjuvant CT (78.8%)	NLR as prognostic factor for DFS and OS	2.85	+ NLR and DFS (HR = 2.63; *p* < 0.001) + NLR and OS (HR = 3.26; *p* < 0.001)	+ NLR and DFS (HR = 2.13; *p* = 0.008) + NLR and OS (HR = 2.69; *p* = 0.001)
Pistelli 2015	90 TNBC patients	NS	NLR as prognostic factor for DFS	3	+ NLR and DFS (*p* = 0.002) + NLR and OS (*p* = 0.003)	+ NLR and DFS (HR = 5.15; *p* = 0.03) + NLR and OS (HR = 6.16; *p* = 0.01)
Lee 2019	358 TNBC patients	Adjuvant CT (86.6%) : anthracyclines (50.9%), anthracyclines + taxanes (22.4%), others (26.7%) NACT (14%): anthracyclines + taxanes (64%), anthracyclines (36%)	NLR as prognostic factor for DFS and OS	3.16	+ NLR and DFS (HR = 2.11; *p* = 0.036) + NLR and OS (HR = 2.97; *p* = 0.003)	- NLR and DFS (*p* = 0.14) + NLR and OS (HR = 3.15; *p* = 0.009)
Patel 2019	126 TNBC patients	NACT (31.7%) or adjuvant CT (52.4%) or both (4.8%)	NLR as prognostic factor for DFS and OS	NLR: 3 (based on previous studies)	- NLR baseline and DFS (*p* = 0.77) - NLR baseline and OS (*p* = 0.23)	
Liu 2016	318 HR negative patients including 157 Her2 positive (49.4%) 161 Her2 negative (50.6%)	adjuvant CT (81.5%) or NACT (17.6%) or none (0.9%)	NLR as prognostic	3	+ NLR and DFS (HR = 2.37; *p* < 0.001) + NLR and OS (HR = 3.09; *p* < 0.001)	+ NLR and DFS (HR = 1.89; p < 0.001) + NLR and OS (HR = 3.09; p < 0.001)

NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, PCR: pathological complete response, DFS: disease free survival, OS: overall survival, CT: chemotherapy, NACT: neoadjuvant chemotherapy, ER: estrogen receptor, PR: progesterone receptor, BCSS: breast cancer specific survival, OR: odd ratio, HR: hazard ratio, BC: breast cancer, TNBC : triple negative breast cancer

3.1.1.2.1 Results on DFS

3.1.1.2.1.1 Studies including all molecular subtypes

Seventeen studies had analysis on DFS (33–47). In univariate analysis, 82% of them (N = 14) reported that NLR was correlated with DFS (34,35,37–42,44–46,46,47). Thirteen papers reported results with multivariate models (34,35,37–42,44,46–48) and 8 of them (61.5%) showed that NLR was an independent prognostic factor for DFS (34,37–40,46,48).

3.1.1.2.1.2 Studies with specific molecular subgroups

Four studies reported data on patients with TNBC (49–52). Three out of four (75%) showed that high NLR was correlated to shorter DFS in univariate analyses (49–51). In multivariate analyses two studies showed a statistically significant correlation between NLR and DFS in TNBC patients receiving adjuvant CT (49,50).

Liu *et al* (53) studied patients with hormone receptor negative BC. They found a correlation between NLR and DFS as well in univariate than in multivariate analysis (HR = 1.89; 95%CI 1.42-2.51; $p < 0.001$).

3.1.1.2.1.3 Subgroup analyses

Many studies reported subgroup analyses based on stage, molecular or pathological subtypes. Five studies tried to differentiate if results were different according to molecular subtypes (32,38,39,44,46). Cho *et al* (44) found that NLR was correlated with DFS (and to disease specific survival) only in luminal cancer; Noh *et al* (32) found the same results for luminal A cancer; whereas for Hong *et al* and for Jia *et al* (38,39) NLR was correlated with DFS only in TNBC. Finally, in Geng *et al* subgroup analyses (46), correlation between NLR and DFS was found for all molecular subtypes.

Cho *et al* showed that in patients with lymph node invasion, NLR was correlated to DFS, but only in univariate analysis (44).

Two authors (45,46) showed that NLR was correlated to DFS in early stage (I and/or II according to AJCC) but not in stage III BC.

3.1.1.2.2 Results on OS and BCSS

3.1.1.2.2.1 Studies including all molecular subtypes

Ten studies reported data on NLR and OS in patients receiving adjuvant treatment (33,34,36–39,41,42,45,47). Out of them, 6 (60%) found a correlation in univariate analysis (34,36,37,39,41,45).

Five authors had multivariate analyses on NLR and OS (34,36,37,39,41) and 4 of them (80%) found that NLR was an independent prognostic factor for OS (34,36,37,39).

Three studies reported data on NLR and BCSS (32,35,44). All of them showed correlation between these two factors in univariate analyses and two out of three (66%) showed that NLR was an independent prognostic factor for BCSS (32,35).

3.1.1.2.2.2 Studies including specific molecular subtypes

Four studies reported data on patients with TNBC and studied OS according to NLR (49–52). Three out of four (75%) showed that high NLR was correlated to shorter OS in univariate analysis (49–51). In multivariate analysis three studies (out of three) showed a statistically significant correlation between NLR and OS in TNBC patients receiving adjuvant CT (49–51).

Liu *et al* studied patients with hormone receptor negative BC (53). They found a correlation between NLR and OS as well in univariate than in multivariate analyses (HR = 3.09; 95%CI 2.35-4.06; $p < 0.001$).

3.1.1.2.2.3 Subgroup analyses

Yao *et al* (36) found that luminal A and TNBC were the two intrinsic subtypes in which NLR is correlated to OS, whereas Jia *et al* (39) found that NLR is correlated to OS only in the TNBC subgroup.

3.1.1.2.3 Conclusion on NLR as prognostic factor in patients receiving adjuvant treatment

Twenty three papers reported data on NLR as prognosis factor in patients receiving adjuvant treatment (32–53). In those papers a total of 29 multivariate analyses were conducted and 21 one of them (72.4%) report a correlation between NLR and survival (32,34–40,46,48–51,53). Eleven out of 17 analyses (65%) found a positive correlation between NLR and DFS (34,37–40,46,48–50,53), 8 out of 9 analyses (89%) found a positive correlation between NLR and OS (34,36,37,39,49–51,53) and 2 out of 3 analyses (66%) found a positive correlation between NLR and BCSS (32,35). A total of 18 153 patients were enrolled in these studies. Table 4 summarizes multivariate analyses and adjustment factors.

Table 4: Multivariate models (results and adjustment factors) for patients receiving adjuvant treatment

All molecular subtypes					
		DFS	OS	BCSS	Total
Number of multivariate models		13	5	3	21
Number of unique patients		9333	4597	1879	15809
NLR significantly associated with n(%)		8 (61.5%)	4 (80%)	2 (66%)	14 (66%)
Adjustment factor (%)					
	T	77	80	33	
	N	70	60	100	
	AJCC stage	38	40	NI	
	Age	31	20	67	
	Menopausal status	23	NI	NI	
	Hormone receptors	23	NI	67	
	Her2 status	8	NI	NI	
	Molecular subtype	54	80	NI	
	Histological grade	38	20	NI	
	LVI	8	NI	33	
	Perineural invasion	NI	NI	33	
	Ki67	8	NI	NI	
	Multifocality	8	NI	NI	
	Adjuvant CT	15	20	NI	
	Endocrine therapy	8	NI	NI	
	Use of NSAIDS	8	20	NI	
	PLR	15	40	33	
	LMR	15	20	33	
	MCH	8	NI	NI	
	RDW	NI	20	NI	
	dNLR	8	NI	33	
TNBC					
		DFS	OS		Total

Number of multivariate models		3	3		6
Number of unique patients		854	854		1708
NLR significantly associated with n(%)		2 (66%)	3 (100%)		5 (83%)
Adjustment factor (%)					
	T	67	67		
	N	67	67		
	AJCC stage	33	33		
	Age	100	67		
	Menopausal status	33	33		
	Histological subtype	33	33		
	Histological grade	67	67		
	Ki67	33	67		
	Necrosis	33	33		
	LVI	67	67		
	Type of surgery	33	33		
	Adjuvant CT (*vs* NACT)	33	33		
	Adjuvant radiotherapy	33	33		
	Cancer recurrence	NI	33		
HR negative					
		DFS	OS		Total
Number of multivariate models		1	1		2
Number of unique patients		318	318		636
NLR significantly associated with n(%)		1 (100%)	1 (100%)		2 (100%)
Adjustment factor (%)					
	T	100	100		
	N	100	100		
	Age	100	100		
	Histological grade	100	100		
	Her 2 status	100	100		
	PLR	100	100		
All studies					
		DFS	OS	BCSS	Total
Number of multivariate models		17	9	3	29
Number of unique patients		10505	5769	1879	18153
NLR significantly associated with n(%)		11 (65%)	8 (89%)	2 (66%)	21 (72.4%)

CT: chemotherapy, DFS: disease free survival, OS: overall survival, BCSS: breast cancer specific survival, NLR: neutrophil to lymphocyte ratio, NSAIDs: non-steroidal anti-inflammatory drugs, LMR: lymphocyte to monocyte ratio, MCH: mean corpuscular hemoglobin, NMR: neutrophil to monocyte ratio, RDW: red cell distribution width, dNLR: derived NLR, PLR: platelet to lymphocyte ratio, LVI: lympho-vascular invasion, NACT: neoadjuvant chemotherapy, NI: not indicated

3.1.1.2.4 Results on other IBM

Eleven studies reported results on IBM other than NLR. PLR was found to be correlated to DFS in 4 analyses (41,43,44,53) out of six (66.6%) studying this

correlation (33,36,41,43,44,53) and to OS in two analyses (41,53) out of 4 (50%) studying this correlation (33,36,41,53). It was found to be correlated to DSS in Cho *et al*'s work (44). Four authors (41,43,44,53) reported data on PLR with multivariate analyses and 75% of them found that PLR was an independent prognosis factor for DFS (41,43,44), 50% (one out of two) found a correlation between PLR and OS (41) and 100% for DSS (but it was reported in only one study) (44).

Two studies reported data on dNLR (derived NLR, calculated as neutrophil over white blood cells [WBC] minus neutrophils) and both found correlation between dNLR and DFS or OS or DSS in univariate analyses (37,44) but not in multivariate analyses (44).

Jia *et al* (39), Takeuchi *et al* (43) and Cho *et al* (44) studied LMR as prognosis factor. Jia *et al* and Cho *et al* found a correlation between LMR and DFS, OS and DSS in univariate analysis. In multivariate analyses, no correlation was found between LMR and survival.

Lymphocyte count and survival was studied in 4 papers (33,44,47,52). Lymphocyte count was correlated to DFS only in one analysis out of 4 (25%) (44), was never found to be correlated to OS an was found to be correlated to DSS in one analysis (25%) (44). No authors did multivariate analyses on lymphocyte count and survival.

Finally, two authors (33,44) showed that there was no correlation between neutrophil count, platelet count, monocyte count and survival. Cihan *et al* (33) also reported no correlation between white blood cell count, eosinophil cell count, basophil cell count and survival in univariate analyses.

3.1.2 Patients with advanced breast cancer (Table 5)

We identified 8 studies that reported data on NLR as prognostic factor in metastatic BC patients (54–61). Four articles (50%) studied cancer of all molecular subtypes (54,56–58), two focused on Her2 positive patients (55,61), one on TNBC (60) and one on hormone receptor positive patients receiving hormone therapy as initial drug therapy (59).

Table 5: Articles including data on NLR as prognosis factor in metastatic breast cancer patients

Author	Number of patients	Treatment received	Primary objective	Cut off	Results on primary objectives (univariate analysis)	Results on multivariate models
Iwase 2017	**89 patients** with recurrent BC following surgery including 31 ER+ Her2- (35%) 20 ER+ Her2+ (22%) 14 Her2 type (16%) 24 TNBC (27%)	NS	NLR and prognosis	3 (based on previous studies)	+ NLR and OS (HR =2 .68; $p < 0.05$)	+ NLR and OS (HR = 2.93; $p > 0.05$)
Araki 2018	**51 Her2 positive patients** including 14 ER+ (47%) 5 PR+ (17%)	pertuzumab and trastuzumab combined with eribuline (ERI) (n=30) or nab-paclitaxel (Nab-PTX) (n=21)	blood based parameters prognostic	NLR: 2 (median values)	- NLR and PFS	
Miyagawa 2018	**85 patients** including 62 ER+ (73%) 39 PR+ (46%) 4 Her2 positive (5%)	eribulin (n=59) or nab-paclitaxel (n=26)	NLR and prognosis according to treatment administrated	3 based on previous studies	+ NLR and PFS eribulin group (HR = 0.37; p = 0.003) - NLR and PFS in nab-paclitaxel group (p = 0.84) - NLR and OS eribulin group (p = 0.058) - NLR and OS in nab-paclitaxel group (p = 0.15)	+ NLR and PFS in eribulin group (HR = 0.39; p = 0.007)
De Sanctis 2018	**71 patients** including 53 hormone receptor+ (75%) 8 Her2 positive (11%) 11 TNBC (15%)	eribulin (after 2 to 5 previous lines of CT)	NLR as prognostic factor	2,5-4-5,5	- NLR and PFS ($p > 0,5$) for any cut off	
Takuwa 2018	171 patients including 93 ER+ Her2 negative (54.4%) 23 ER+ Her2 positive (13.5%) 20 ER- Her2 positive (11.7%) 28 ER- Her2 negative (16.4%) 7 unknown (4.0%)	NS	NLR as prognostic factor	1.9	+ NLR and OS (33 *vs* 79 months, p = 0.004)	+ NLR and OS (HR = 1.75; p = 0.022)

Table 5 (continued)

Author	Number of patients	Treatment received	Primary objective	Cut off	Results on primary objectives (univariate analysis)	Results on multivariate models
Iimori 2018	**34 patients** receiving ET as initial drug therapy including 4 Her2 positive (12%)	Endocrine therapy: letrozole (58.8%); anastrozole (20.6%); tamoxifen (with/without LHRH) (17.7%); exemestane (2.9%)	NLR predictive of response to endocrine therapy and prognosis	3 based on previous studies	+ NLR and PFS (HR = 3.94; p = 0.016) + NLR and OS (p = 0.013) + NLR and time to treatment failure (p = 0.031)	+NLR and PFS (HR = 3.93; p = 0.008)
Vernieri 2018	**57 TNBC** patients	Platinum based CT: Carboplatin-taxol (84%) or carboplatin-gemcitabin (16%) First line (88%) or second line (12%)	NLR as prognostic factor	2.5 based on previous studies	+ NLR and PFS (HR = 3.25; p < 0.001)	+ NLR and PFS (HR = 2.65; p = 0.004)
Imamura 2019	**53 Her2 positive** patients	TDM-1	NLR as prognostic factor	2,56	+ NLR and PFS (HR = 0.23; p < 0.001) + NLR and OS (HR = 0.38; p = 0.0296)	+ NLR and PFS (HR = 0.27; p = 0.0019) + NLR and OS (HR = 0.35; p = 0.018)

NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, PCR: pathological complete response, DFS: disease free survival, OS: overall survival, ER: estrogen receptor, PR: progesterone receptor, BCSS: breast cancer specific survival, OR: odd ratio, HR: hazard ratio, BC: breast cancer, ET: endocrine therapy, TNBC: triple negative breast cancer

For NLR, the cut off was set between 1.9 and 3 (for all of the studies, the cut off value was based on previous studies). Number of patients enrolled in each study varied between 34 and 171. Six studies (75%) reported data on Asian populations (54–56,58,59,61).

3.1.2.1 Results on PFS

3.1.2.1.1 Studies including all molecular subtypes

Two studies reported data on NLR and PFS (56,57) and one of them (50%) showed that NLR was an independent prognostic factor for PFS (HR = 0.39; 95%CI 0.18-0.78; $p < 0.001$) (56).

3.1.2.1.2 Studies including only specific molecular subtypes

Vernieri *et al* (60) studied TNBC subtype and found that NLR was an independent prognostic factor for PFS for their population of 57 patients (HR = 2.65; 95%CI 1.36-5.18; $p = 0.004$).

In the two papers interested in patients with Her2 positive tumors (55,61), only one of them found a correlation between NLR and PFS in multivariate analysis (HR = 0.27; 95%CI 0.10-0.63; $p < 0.001$) (61).

Iimori *et al* (59) found that NLR was an independent prognostic factor for PFS in their population of patients with hormone receptor positive BC receiving endocrine therapy as initial drug therapy (HR = 3.93; 95%CI 1.4-10.84; $p = 0.008$).

3.1.2.2 Results on OS

3.1.2.2.1 Studies including all molecular subtypes

Three studies reported data on NLR and OS (54,56,58) and two of them (66%), written by Iwase *et al* (54) and Takuwa *et al* (58) found that NLR was an independent prognostic factor for OS in patients with metastatic BC.

3.1.2.2.2 Studies including only specific molecular subtypes

Imamura *et al* (61) studied NLR and OS in patients with Her2 positive BC and found a correlation between these two factors in univariate and multivariate analyses (HR = 0.35; 95%CI 0.13-0.84; *p* = 0.018).

Iimori *et al* (59) conducted the same analysis on patients with hormone receptor positive BC and found a correlation in univariate analysis (multivariate results not available).

3.1.2.3 Conclusion on NLR as prognostic factor in patients with advanced breast cancer

Six articles reported data with multivariate analyses on patients with advanced BC (54,56,58–61). All (6 out of 6) of the studies analyzing NLR and survival found a significant correlation between these two factors. Data should be handling carefully since not all the studies had multivariate analyses and the populations are very heterogeneous. Table 6 summarizes results on multivariate analyses and adjustment factors.

Table 6: Multivariate models (results and adjustment factors) for patients treated for advanced BC

All molecular subtypes			
	PFS	OS	Total
Number of multivariate models	1	2	3
Number of unique patients	85	260	345
NLR significantly associated with n(%)	1 (100%)	2 (100%)	3 (100%)
Adjustment factor (%)			
Menopausal status	NI	50	
BMI	NI	50	
Molecular subtype	NI	50	
LDH	NI	50	
Complete response	NI	50	
Primary stage IV	NI	50	
Number of metastatic sites	NI	50	
Visceral metastasis sites (≥ 2 *vs* <2)	NI	50	
Previous CT	100	NI	
HR +			
	PFS		Total
Number of multivariate models	1		1
Number of unique patients	34		34
NLR significantly associated with n(%)	1 (100%)		1 (100%)
Adjustment factor (%)			
Objective response to endocrine therapy	100	NI	
TNBC			

		PFS		Total
Number of multivariate models		1		1
Number of unique patients		57		57
NLR significantly associated with n(%)		1 (100%)		1 (100%)
Adjustment factor (%)				
	Visceral metastasis	100	NI	
	Maintenance CT	100	NI	
	Previous exposure to taxanes	100	NI	
	PLR	100	NI	
Her 2 positive				
		PFS	OS	Total
Number of multivariate models		1	1	2
Number of unique patients		53	53	106
NLR significantly associated with n(%)		1 (100%)	1 (100%)	2 (100%)
Adjustment factor (%)				
	Disease control during 1st line	100	100	
	Number of metastatic sites	100	100	
All patients				
		PFS	OS	Total
Number of multivariate models		4	3	7
Number of unique patients		229	313	542
NLR significantly associated with n(%)		4 (100%)	3 (100%)	7 (100%)

CT: chemotherapy, PFS: progression free survival, OS: overall survival, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, BMI: body mass index, NI: not indicated

3.1.2.4 Results for other IBM

Three articles had data on other IBM as prognostic factors for survival in advanced BC (55,60,61). In univariate analysis, PFS was related to ALC, to PLR and to LMR in some analysis (55,60), but contradictory results showed no correlation between PLR and PFS (61). Vernieri *et al* (60) reported multivariate analysis and found that PLR was an independent prognostic factor for PFS. One analysis showed that PLR was not a prognostic factor for OS (61).

3.2 Toxicity (Table 7)

We identified 4 articles that reported data on IBM and treatment-related toxicity (62–65) as primary objective. Only one study analyzed the relation between NLR and toxicity in a cohort of BC (Yamanouchi *et al* (65)). The three others were interested in lymphopenia (defined as

lymphocytes value < 0.7 G/L) in a cohort of different cancer types (including BC). Two studies evaluated a French population (62,63), while the 2 other ones focused on Asian patients (64,65).

In 2001, Ray Coquard *et al* (62) studied predictive factors for early death after CT (defined as death within one month after the administration of cancer CT) in a prospective study and found, in a group of 1051 patients with different types of cancer (including 756 [33%] BC patients), that lymphocyte count at day 1 < 0.7 G/L was predictive for early death cancer as well in univariate than in multivariate models (OR = 3.1 ; 95%CI 1.8-5.8; $p < 0.001$).

The same authors published a second article in 2003 (63) were they evaluated if lymphocyte count < 0.7 G/L at day 1 was predictive for febrile neutropenia (FN). They evaluated three cohorts of patients (including the cohort used for their previous work) accounting for 950, 321 and 329 patients, of whom 24%, 33% and 42% of them were affected by BC, respectively. They found that, in the largest cohort of patients, lymphocyte count < 0.7 G/L at day one was predictive for FN in univariate and multivariate analyses (OR = 1.75; 95%CI 1.49-4.8; $p = 0.02$).

A Korean study, written by Choi *et al* (64), performed the same evaluation in a group of 82 patients (including 11 [13%] BC patients) receiving their first course of CT. They found no correlation between lymphopenia at day one and risk of FN. However, considering the limited number of BC patients in this series, no definitive conclusion could be drawn from this publication.

Yamanouchi *et al* (65) were the only ones to study, in a cohort of 67 patients with BC, the relationship between peripheral neuropathy and NLR, PLR or MLR in patients receiving at least 4 cycles of docetaxel (75 mg/m^2). They found no correlation between these three IBM and the occurrence of peripheral neuropathy.

Table 7: Articles including data on IBM as predictive factor of toxicity in breast cancer patients

Author	Number of patients	Population of interest	Treatment received	Primary objective	Cut off	Results on primary objective (univariate results)	Results on multivariate model
Ray Coquard 2001	1051	first line CT all cancers (BC, colon, ovary, head and neck, lung, other)	NS	to establish a risk model for early death after CT (defined as death within a month after the administration of CT)	lymphocytes < 0.7 G/L	predictive of early death: day 1 lymphocyte count < 0.7 G/L (p < 0.01) day 1 platelet count < 150 G/L (p = 0.01)	predictive of early death: d1 lymphocytes < 0.7 G/L (OR = 3.1)
Ray Coquard 2003	3 groups : -950 patients in groupe CLM-1996 - 321 patients in Elypse 1 - 329 patients in Elyspe 0	all cancers (BC, colon-rectum, ovary, head and neck, lung, lymphoma, myeloma, sarcomas, germ cells tumors, others) receiving CT (regardless of previous course)	NS	to investigate a risk model for FN using only day 1 blood cell count and to compare the day 1 and day 5 risk model	lymphocytes < 0.7 G/L	in CLB-1996 cohort: + lymphocytes d1 and FN (p = 0.05) lymphocytes d5 and FN data not available in Elypse 1 cohort: - lymphocytes d1 and FN (p = 0.18) + lymphocytes d5 and FN (p < 0.01) in Elypse 0 cohort: - lymphocytes d1 and FN (p = 0.08) + lymphocytes d5 and FN (p < 0.01)	lymphocytes d1 and FN (OR = 1.75; p = 0.02)
Choi 2003	82	all cancers (non Hodgkin lymphoma, stomach cancer, BC, NSCLC, hepatobiliary cancer, sarcoma, colorectal cancer and others) receiving first course of CT	NS	to evaluate lymphocyte count at day 1, day 3 and day 5 as a way to identify patients at risk of FN	lymphocytes < 0.7 G/L and lymphocytes < 0.5 G/L	for lymphocytes ≤ 0,5 G/L: - d1 and FN (p = 0.33) + d3 and FN (p < 0.01) + d5 and FN (p = 0.023) for lymphocytes ≤ 0,7 G/L: - d1 and FN (p = 0.05) + d3 and FN (p = 0.01) + d5 and FN (p < 0,01)	d5 lymph ≤ 0,7 G/L and NF (OR = 19.0 p = 0.01)
Yamanouchi 2017	67	BC, all stages (only 6% stage IV)	Docetaxel 75 mg/m^2 at least 4 cycles	to elucidate the relationship between peripheral neuropathy (PN) and NLR, PLR and MLR	median NLR of patients with or without toxicity analyzed	no correlation between the NLR, PLR, or MLR before or at the first or third cycle and the occurrence of PN	

CT: chemotherapy, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, MLR: monocyte to lymphocyte ratio, OR: odd ratio, BC: breast cancer, FN: febrile neutropenia, PN: peripheral neuropathy

4. CONCLUSION

We report here a comprehensive, exhaustive overview of the published literature regarding NLR as a predictive and / or prognostic factor in BC patients.

NLR appears to be a reliable prognostic factor in the adjuvant BC setting, since 21 analyses out of 29 (72.4%) with reported multivariate data found an independent correlation between NLR and survival (DFS, BCSS and / or OS) (32,34–40,46,48–51,53).

Results are more controverted for patients with localized disease receiving NACT since only two studies out of four (50%) found a correlation between NLR and DFS (25,30) and one study out of two (50%) found a correlation between NLR and OS (30). The only study that analyzed NLR and BCSS found a significant correlation (25). In the same NACT-treated population, conclusions on NLR and PCR can't be established since only one study out of two (50%) found a correlation between these two factors (31). Some heterogeneity in the impact of NLR in this setting could be linked to variable impacts of this factor based on molecular subtypes, as the only positive study evaluated only TNBC patients.

This lack of significant association in the NACT setting could be also linked to analyses with smaller populations. Indeed, the total number of patients enrolled in selected studies analyzing NACT was 1558 *versus* 18153 patients analyzed in studies focusing on patients with early BC receiving adjuvant treatment.

Fewer data have been published for patients with metastatic BC, but NLR appears to be a good prognostic factor for PFS and OS in this population, although studies are hard to compare since the population are very heterogeneous (54,56,58–61). Population of interest was different for each study analyzed, either by the molecular features of BC analyzed or by the treatment received or by the number of previous lines of CT received before. Therefore, no conclusion can be made on IBM as prognosis factor in patients with metastatic BC.

Only very few studies are focused on NLR or lymphopenia as predictive factor of CT-related toxicity (62–65). Lymphopenia at day one appears to be correlated with early death after CT (62), but no definitive conclusion could be made for BC patients since the population studied included various cancer types, and no specific subgroup analysis has been performed in the BC subgroup. Lymphopenia at day one was inconsistently correlated to febrile neutropenia

(two studies diverge on results (63,64)) and NLR was not correlated to peripheral neuropathy in patients receiving docetaxel (65). Other studies with larger population should be conducted in order to have more data on NLR or lymphopenia as predictive factor for toxicity.

Considering its worse prognosis and better chemosensitivity, TNBC has been the molecular subgroup the most extensively evaluated, as, out of the studies that we compared in this review, subgroup analyses on TNBC have been reported in 10 analyses (23,24,32,36,38,39,46,53,56). Most of them (80%) found a correlation between NLR and survival in this specific sub group (23,36,38,39,46,53,56), a proportion of positive articles higher than reported in the other subgroups, possibly related to the TNBC specific clinical history.

It is noteworthy, in this overview of the published literature, that majority of the selected studies (33/41) were evaluating a population of Asian patients (23,25,28,30–32,35,36,38,39,42–44,46–49,51,53–56,58,59,61,64,65). This demographic variable could be associated with specific molecular and pharmacological features that can induce differences in toxicity and efficacy profiles. Another limitation is linked to the HER2 population, where the notion of anti-HER2 targeted therapy use is inconsistently reported, inducing heterogeneity in survival expectations. Considering these population-based sources of confusion, a large, multi-ethnical study appears mandatory in order to evaluate, worldwide and part of the world by part of the world, the prognostic and predictive value of NLR and other IBM in BC patients.

Another limitation comes from the drugs used in the neoadjuvant or adjuvant regimens as, although most of the studies reported the use of anthracyclines and /or taxanes, only a minority of them (16 out of 34, 47%) declared to use sequential or concomitant anthracyclines and taxanes-based regimens, presently recommended by the international societies. Data on CT regimen were missing for many studies (18 out of 34, 53%).

Lastly, one must keep in mind that the selected studies were retrospective. Even if most of them (> 75%) reported at least one multivariate model in order to reinforce their results, a prospective validation, or the retrospective evaluation in a prospective clinical trial, of these results appears necessary.

In conclusion, NLR appears to be a prognostic factor for DFS and OS in patients with early BC receiving adjuvant CT. Further investigations with prospective studies would help to reinforce

these results. For NACT the correlation between NLR and survival remains unclear since most of the studies failed to show an evidence of independent correlation. Finally, most of the available data show that NLR is not a predictive factor for PCR in patients treated with NACT, however, due to the heterogeneity and / or small sample size of the published data on this topic, dedicated studies are needed.

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Conclusion générale

Ces deux travaux évaluent des marqueurs biologiques de l'inflammation en tant que facteurs pronostiques et / ou prédictifs de réponse histologique à la chimiothérapie ou de risque de toxicité induites par la chimiothérapie. Ces marqueurs sont très intéressants car disponibles facilement en pratique courante et non couteux. Ils pourraient ainsi nous aider dans la prise de décision quant aux traitements à administrer à nos patients.

Dans notre premier article, qui est une étude rétrospective sur une population de 280 patientes traitées à l'ICM pour un cancer du sein localisé et recevant une chimiothérapie néoadjuvante, nous avons montré en analyse multivariée, que le PLR est un facteur pronostique de survie sans récidive (HR = 1.91; IC95% = 1.15-3.16 ; p = 0.012) ainsi qu'un facteur pronostique de survie globale (HR = 1.83; IC95% = 1.03-3.24 ; p = 0.039). Ainsi un PLR élevé au diagnostic prédirait un risque plus élevé de récidive et de décès. Cette étude montre également qu'un NLR élevé au diagnostic est un facteur prédictif indépendant de neutropénie fébrile au cours de la chimiothérapie (OR = 0.28; IC95% = 0.13-0.58 ; p = 0,001). Aucun marqueur biologique de l'inflammation n'a été retrouvé comme prédictif de réponse histologique complète après chimiothérapie néoadjuvante dans la population globale. Lorsque l'on s'intéresse aux sous-groupes moléculaires, il apparait que chez les patientes ayant un cancer du sein triple négatif (récepteurs hormonaux négatifs et Her2 négatif) un faible taux de leucocytes au diagnostic (< 6.75 G/L) serait prédictif d'une réponse histologique complète. A notre connaissance, nous rapportons ici la deuxième plus grande série évaluant ces marqueurs biologiques de l'inflammation en situation néoadjuvante. Notre population est homogène, avec des patientes ayant reçu les traitements recommandés par les sociétés savantes et nous disposons d'un long suivi de plus de 6 ans. Nos résultats sont cohérents avec ceux de la littérature.

Dans la revue de la littérature nous nous sommes surtout intéressés au NLR, puisque c'est le biomarqueur qui a été le plus étudié. En situation néoadjuvante, tous sous-groupes moléculaires confondus, la majorité des articles ne retrouvaient pas de corrélation entre ce ratio et la survie sans récidive (66%), la survie globale (100%) ou la réponse histologique complète après traitement (100%). Une seule étude retrouvait une relation statistiquement significative entre le NLR et la survie spécifique (100%). En situation adjuvante, la majorité des études (72.4%) mettaient en évidence un lien entre le NLR et la survie (65% pour la survie sans récidive, 89%

pour la survie globale et 66% pour la survie spécifique). En situation métastatique ou localement avancée, le NLR est un facteur pronostique dans tous les articles retenus (cependant avec des populations de faibles effectifs et très hétérogènes). Enfin, notre revue s'est également intéressée à la capacité de ces biomarqueurs de prédire les toxicités liées à la chimiothérapie. Seuls 4 articles rapportent de telles données et leurs résultats divergent. La lymphopénie (lymphocytes < 0.7 G/L) au diagnostic serait prédictive d'un décès précoce (< 1 mois) après la chimiothérapie et de neutropénie selon les études du Dr Ray Coquard, mais pas selon l'étude de Choi *et col.* Aucun lien n'a pu être démontré entre les marqueurs biologiques de l'inflammation et la survenue d'une neuropathie périphérique après un traitement par docetaxel.

Pour pouvoir conclure quant à la validité clinique et l'utilité clinique de ces biomarqueurs de l'inflammation dans le cancer du sein, des études prospectives ou au minimum rétrospectives sur des données issues d'études prospectives, sont nécessaires.

SERMENT D'HIPPOCRATE

- *En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure, au nom de l'Etre suprême, d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine.*

- *Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail.*

- *Admis (e) dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.*

- *Respectueux (se) et reconnaissant (e) envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.*

- *Que les hommes m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert (e) d'opprobre et méprisé (e) de mes confrères si j'y manque.*

Résumé

Introduction :
Les marqueurs biologiques de l'inflammation (MBI) tels que le taux de leucocytes, lymphocytes, neutrophiles ou les ratios tels que les ratios de neutrophiles sur lymphocytes (NLR) ou plaquettes sur neutrophiles (PLR) émergent comment nouveaux facteurs pronostiques et prédictifs de réponse histologique complète ou de toxicité liée à la chimiothérapie (CT). De plus en plus d'études les ont évalués, avec des résultats divergents.

Matériel et méthodes :
Nous avons réalisé une étude rétrospective sur 280 patientes suivies pour un cancer du sein localisé recevant une CT néoadjuvante. Les MBI avant traitement ont été recueillis ainsi que la réponse histologique, la survenue de toxicités, la récidive et la survie.
Nous avons également réalisé une revue systématique de la littérature portant sur le NLR en tant que facteur pronostic et prédictif chez des patientes ayant un cancer du sein localisé (recevant une CT néoadjuvante d'une part et un traitement adjuvant d'autre part) ou métastatique.

Résultats :
En analyse multivariée, un PLR élevé (≥ 150) était corrélé à une moins bonne survie sans récidive et survie globale (Hazard ratio [HR] = 1.91 ; IC95% = 1.15-3.16 ; p = 0.012 et HR = 1.83 ; IC95% = 1.03-3.24 ; p = 0.039, respectivement). Le NLR était un facteur prédictif indépendant de neutropénie fébrile (Odds ratio = 0.28 ; IC95% = 0.13-0.58 ; p = 0,001). Aucun MBI n'était prédictif de réponse histologique complète.

Conclusion :
Le PLR est un facteur pronostic de survie dans notre population, alors que le NLR est un facteur prédictif de neutropénie fébrile. Ces résultats sont concordants avec ceux décrits dans notre revue de la littérature.

Mots clés : cancer du sein, marqueurs biologiques de l'inflammation, facteurs prédictivfs, facteurs pronostiques, réponse histologique complète, toxicité liée à la chimiothérapie.