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Albumin-To-Alkaline Phosphatase Ratio as a New Early Predictive Marker of Axillary Response in Breast Cancer Patients Undergoing Neoadjuvant Chemotherapy: A Pilot Study

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Abstract: *Background and Objectives:* The Albumin-to-Alkaline Phosphatase ratio (AAPR) is an easily applicable and cost-effective marker investigated as an outcome predictor in solid cancers. Preliminary evidence in breast cancer suggests that a low AAPR correlates with a poor response to neoadjuvant chemotherapy (NAC) in primary tumors. However, data regarding the axillary response are lacking. This study aims to evaluate whether the AAPR can predict the axillary response in initially nodal-positive (cN+) breast cancer patients undergoing NAC. *Materials and Methods:* Clinical and biochemical variables of cN+ breast cancer patients undergoing NAC were collected. Pre-NAC albumin and alkaline phosphatase serum values were utilized in the AAPR calculation. Fisher's exact test was performed to identify differences between the two groups of patients (high and low AAPR according to the cut-off reported in the literature). The primary outcome was the nodal pathologic complete response (pCR) rate in the two groups of patients. *Results:* Nodal pCR was achieved in 20/45 (44.4%) patients. A total of 36/45 (80%) patients had an AAPR > 0.583. Among patient and tumor characteristics, the only statistically significant difference between the two groups was the axillary pCR between the low and high AAPR groups (p -value = 0.03, OR = 0.129, 95% CI = 0.00–0.835). *Conclusions:* This pilot study suggests that the pre-treatment AAPR might be an early predictor of axillary response in cN+ breast

cancer patients undergoing NAC. This result justifies further investigation in larger prospective trials to validate this finding.

Keywords: albumin-to-alkaline phosphatase ratio; axillary lymphadenectomy; breast cancer; neoadjuvant chemotherapy; sentinel lymph node biopsy

1. Introduction

Breast cancer is ranked among the leading causes of cancer-related mortality worldwide, affects millions of women, and thus is a major global health burden [1]. The surgical treatment in the non-metastatic setting includes two compartments, breast and axilla, in a multimodal and interdisciplinary approach. In the last decades, axillary surgery has no longer been considered a therapeutic procedure in the majority of cases, shifting towards becoming purely a staging and prognostic procedure, able to provide an indication of further therapy required.

Nearly one-third of those diagnosed with primary breast cancer has also lymph node involvement at the time of diagnosis (cN+) [2]. As for the primary breast tumor, where NAC plays a pivotal role in reducing the tumor burden and allows a surgical de-escalation from mastectomy to breast conservative surgery [3], NAC in the axillary compartment aims to provide a response that allows a minimally invasive procedure instead of a full axillary lymphadenectomy. The rate of axillary lymph node response after NAC depends on tumor subtype, and the pathologic complete response (pCR) varies between 16% in hormonal receptor-positive HER-2-negative breast cancer, 70% in triple-negative breast cancer, and up to 80% in HER-2-positive breast cancer [4]. There is no international consensus on axillary management after NAC in cN+ breast cancer. The reason that the sentinel lymph node biopsy is not universally accepted after NAC instead of axillary lymphadenectomy is due to the high false negative rate in this setting, which exceeds 10% in most international prospective validation studies [5–11]. In order to improve the performance of this technique, NCCN guidelines suggest collecting at least 3 sentinel lymph nodes and/or adopting more than one tracer [12]. The false negative rate (FNR) of sentinel lymph node biopsy decreases significantly with the number of sentinel lymph nodes removed (2 sentinel lymph nodes = 12% FNR; 3 sentinel lymph nodes = 4% FNR) [13]. However, the more lymph nodes we remove, the higher the morbidity. Therefore, the more lymph nodes we remove, the closer we obtain to an axillary lymphadenectomy (which is commonly defined as the removal of at least 10 nodes) both in terms of FNR and in terms of morbidity. Additionally, it is not always technically feasible to obtain at least 3 sentinel lymph nodes since even when the mapping is performed correctly, the tracer can detect a maximum of one sentinel lymph node. Even when dual tracers are adopted, the false negative rate is generally slightly above what is considered the upper acceptable limit of 10%. The selective removal of the metastatic lymph node marked before NAC associated with biopsy of the sentinel lymph node (targeted axillary dissection) represents an “in-between solution” with good surgical performance and low FNR [14]. Evidence on oncological outcomes suggests that both approaches are equally safe in this setting and provide the same prognostic information [15].

Today, TAD is the most common post-NAC axillary surgery in patients with cN+ disease converting to ycN0, followed by sentinel lymph node biopsy (SLNB) alone [16]. Differences in surgical performance and patients’ perspectives are currently under evaluation. The current ongoing AXSANA (EUBREAST-3) study was designed to reduce international heterogeneity and standardize guidelines [17].

Nevertheless, both in the case of sentinel lymph node biopsy and in the case of TAD, the key point for axillary surgical de-escalation remains the identification of which patients may benefit the most from NAC. Predictive models are being investigated, and so far, several independent clinical and histological predictive factors associated with nodal pathologic complete response (pCR) have been identified, with nomograms to predict

axillary status after NAC in cN+ breast cancer patients proposed [3,18–21]. Clinicopathological indicators have also been integrated with laboratory markers in evaluating response to NAC [22–25]. In order to increase the accuracy of these predictive tools, additional biomarkers are needed and are, therefore, currently under investigation.

The Albumin-to-Alkaline Phosphatase ratio (AAPR) is an easily applicable laboratory marker shown to predict pCR after NAC as well as oncologic outcomes in various solid tumors, including glioblastoma, bladder, renal, cervical, gastric, hepatic, gallbladder, and pulmonary cancer. A low AAPR is associated with a less favorable outcome and inadequate response to NAC [26].

In breast cancer, three retrospective studies have investigated AAPR as a predictor of response to NAC in the primary tumor and a predictor of overall survival with promising results [27–29]. However, none of them investigated the AAPR as a selective predictor of axillary nodal response. The aim of this pilot study is to investigate whether the AAPR can predict pCR in cN+ breast cancer patients receiving NAC.

2. Materials and Methods

2.1. Study Design

A retrospective analysis including cN+ breast cancer patients undergoing NAC has been performed. All patients have been tested for Albumin and Alkaline Phosphatase, and the AAPR has been calculated. According to the cutoff determined in literature in a primary tumor setting [27], the patients have been divided into 2 groups (above and below the cutoff). Patient and tumor characteristics and pathological responses have been analyzed between the two groups.

2.2. Study Population and Ethics Approval

The population eligible for inclusion comprised patients with cN+ breast cancer treated at the Centro di Senologia della Svizzera Italiana (CSSI), Ente Ospedaliero Cantonale (EOC), between January 2016 and January 2023. The inclusion criteria were as follows: (1) clinical and pathological diagnosis of breast cancer; (2) initially cN+ disease; (3) non-metastatic (M0) disease; (4) NAC according to the standard of care followed by documented breast and axillary surgery (TAD/SLND in case of clinical and radiological conversion from cN+ to cN0; ALND in case of no nodal response from NAC); (5) pre-treatment serum albumin and alkaline phosphatase levels; (6) not objection letter recipients patients with only ITCs at the time of axillary staging were not included; micrometastases were considered in the group of no pathologic complete response, given their subsequent required treatment (ALND) as for macrometastases, according with NCCN recommendation [12]. Patients with incomplete information in their medical records for the outcomes extracted were excluded from the analysis. This study was reviewed and approved by the Ethics Committee of Ticino (BASEC ID 2020-01121).

2.3. Data Collection

The medical records of eligible patients were analyzed, and data were extracted from the hospital database. Patient characteristics retrieved for further analysis included age, tumor size, nodal status, histological subtype, histological grade, hormone receptor (HR) status, HER2 status, Ki67 expression, pathological analysis on the primary tumor and axillary lymph node, as well as the pre-treatment serum albumin and alkaline phosphatase levels.

2.4. Statistical Analysis

The continuous variables (age and AAPR) were dichotomized by determining a threshold. The threshold for age was determined by the median value (51, range 24–87). The threshold utilized for the AAPR cut-off was 0.583, according to the results from Qu et al. [27]. AAPR values below the threshold were given a score of 0, and those above the threshold were given a score of 1.

Fisher's exact test was performed to assess the differences in patients and tumor's characteristics between patients with high and low AAPR. The odds ratio (OR) with

the corresponding 95% confidence intervals (CI) were presented. A p -value < 0.05 was considered significant. All statistical analyses were performed using R software Version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS Statistics Version 28 (IBM Corp., Armonk, NY, USA).

3. Results

From January 2016 to January 2023, seventy-eight patients met the inclusion criteria, of which 33 had incomplete medical records and thus were excluded. A total of 45 patients were analyzed in this pilot study (Table 1).

Table 1. Patients and tumor's characteristics.

	Total Number, 45 (100%)	AAPR < 0.583, n = 9	AAPR \geq 0.583, n = 36	p -Value Fisher's Exact T.	OR with 95% CI
Age (median = 51)					
<median	23 (51.1%)	3 (6.7%)	20 (44.4%)		
\geq median	22 (48.9%)	6 (13.3%)	16 (35.6%)	0.284	0.416 (0.073; 1.906)
Histological type					
ductal	39 (86.7%)	8 (17.8%)	31 (68.9%)		
other	6 (13.3%)	1 (2.2%)	5 (11.1%)	1.000	1.175 (0.149; 34.343)
cT					
T1–2	30 (66.7%)	4 (8.9%)	26 (57.8%)		
T3–4	15 (33.3%)	5 (11.1%)	10 (22.2%)	0.135	0.319 (0.063; 1.493)
cN					
N1	31 (68.9%)	6 (13.3%)	25 (55.6%)		
N2–3	14 (31.1%)	3 (6.7%)	11 (24.4%)	1.000	0.867 (0.183; 5.014)
Histological grade					
1–2	10 (22.2%)	1 (2.2%)	9 (20%)		
3	35 (77.8%)	8 (17.8%)	27 (60%)	0.659	0.421 (0.015; 2.897)
Hormone receptor status					
negative	12 (26.7%)	2 (4.4%)	10 (22.2%)		
positive	33 (73.3%)	7 (15.6%)	26 (57.8%)	1.000	0.778 (0.093; 4.069)
HER2 status					
negative	21 (46.7%)	5 (11.1%)	16 (35.6%)		
positive	24 (53.3%)	4 (8.9%)	20 (44.4%)	0.713	1.537 (0.337; 7.473)
Ki67 expression					
<20	2 (4.4%)	0 (0%)	2 (4.4%)		
\geq 20	43 (95.6%)	9 (20%)	34 (75.6%)	1.000	NA
pCR in primary tumor					
ypT0	22 (48.9%)	2 (4.4%)	20 (44.4%)		
ypT \geq 1	23 (51.1%)	7 (15.6%)	16 (35.6%)	0.135	0.246 (0.030; 1.227)
pCR in lymph nodes					
ypN0	20 (44.4%)	1 (2.2%)	19 (42.2%)		
ypN \geq 1	25 (55.6%)	8 (17.8%)	17 (37.8%)	0.030	0.129 (0.005; 0.835)

The median age of the included participants was 51 years, with a range between 24 and 87 years. The most frequent breast cancer histotype was invasive ductal carcinoma (n = 39, 86.7%). Thirty patients (68.9%) had a clinical tumor stage (cT) of T1–2 at diagnosis, while the other third had a clinical stage of T3–4 (n = 15, 33.3%). Thirty-one patients (68.9%) were cN1, while the others were cN2 or cN3 (n = 14, 31.1%). A histological grade of 1–2 was observed in 10 patients (22.2%), whereas 35 patients (77.8%) were diagnosed with a histological grade of 3. Hormone receptor status was positive in 33 patients (73.3%), while there was no expression of either estrogen or progesterone receptors in 12 patients (27.7%). Twenty-four patients (53.3%) had a positive HER2 status. Only two patients had Ki67 expression below 20% (4.4%). Primary tumor pCR was achieved in 22 patients (48.9%) and nodal pCR in 20 patients (44.4%).

Analyzing the results of Fisher's exact test and the odds ratios of the underlying data found that nodal pCR was significantly lower in the AAPR-low group compared to the AAPR-high group (OR 0.129, 95% CI 0.005–0.835, Fisher's exact test $p = 0.03$). There was no significant difference in all other clinicopathological characteristics between the AAPR-low and AAPR-high groups. Detailed results of the analysis are presented in Table 1.

4. Discussion

Over the last few years, there has been a lot of progress in finding a desirable balance to minimize surgical morbidity while having an optimal oncological outcome. In the case of breast cancer patients with clinical axillary lymph node metastases, the approach has shifted from “not leaving a single potentially affected lymph node in the axilla” (complete lymphadenectomy) to a “pick and choose” approach (sentinel lymph node biopsy/targeted axillary dissection). Ideally, complete axillary lymphadenectomy should be confined to selected patients. Complete axillary lymphadenectomy is associated with higher morbidity as compared to TAD and sentinel lymph node biopsy [30]. Side effects of radical axillary management include paresthesia in the axillary region down to the ipsilateral arm, restriction in the range of motion, as well as lymphedema of the ipsilateral arm caused by dysfunctional lymphatic drainage [19]. The latter is the most feared complication, as the swelling may lead to skin damage and an inability to move, which in turn favors infection (cellulitis) and, ultimately, sepsis [20]. Additionally, lymphedema can also affect subsequent loco-regional treatment, such as radiation therapy. Different options have been developed in order to minimize this adverse event; however, the result is still suboptimal for most patients [31–33].

Following NAC, the systematic removal of lymph nodes from the axilla, usually level I and II, sometimes also including level III, is a surgical procedure confined only to patients who still harbor metastatic disease. In cN+ breast cancer patients converting to ycN0, axillary surgical treatment consists of TAD or sentinel lymph node biopsy in most institutions worldwide. Unfortunately, a considerable percentage (27.6–83.5%, depending on cancer subtype) of cases do not undergo a complete response in the axilla with NAC (ycN+), which is revealed only after NAC by clinical and radiological assessment [3]. In these cases, the recommended surgical management of the axilla remains axillary lymph node dissection.

A priori identification of breast cancer patients who will benefit the most from NAC is of high interest for the patient selection process. In cN+ breast cancer patients undergoing NAC with the sole intent of a subsequent de-escalation, presenting with a predicted low rate of response to NAC at diagnosis, surgery could be performed upfront without further delay as the surgical procedure remains the same in the case of axillary clinical involvement. Chemotherapy could be given in the adjuvant setting rather than in the neoadjuvant setting to avoid delaying surgical therapy in this case.

Tools permitting a reliable calculation of the rate of response to NAC at diagnosis are currently under investigation. Predictive models have been developed to identify breast cancer patients likely to have their lymph node status converted from positive to negative after NAC. Clinical and radiological profiling, as well as pre-treatment laboratory indicators

of response, are currently under investigation in order to identify the subset of patients that will benefit the most from NAC at the time of diagnosis.

Recently, in the same way this study was designed, we demonstrated in a larger series that a low neutrophil–lymphocyte ratio and a low pan-immune-inflammation value predict axillary pCR in cN+ in breast cancer patients undergoing NAC [34].

The current pilot study has shown that there is a significant difference in the rate of axillary pCR to NAC in initially cN+ breast cancer patients with low AAPR compared to high AAPR.

The AAPR itself includes two laboratory markers associated with nutritional status and inflammation. An obvious advantage of laboratory predictors such as the AAPR is that they are easily applicable since the involved laboratory markers are part of standard venous blood sampling and, thus, do not need further invasive or cost-intensive measures.

Albumin is an acute-phase protein synthesized in the liver, which can, therefore, provide information on systemic inflammation, nutritional status, and hepatic function [35]. Hypoalbuminemia in all disease processes correlates with a poor prognosis, higher mortality, and surgical complications. Chronically ill patients, such as cancer patients, often have low albumin levels. The theory that low albumin in chronic illness is caused by TNF and IL-6 (acute-phase proteins) decreasing the synthesis of albumin is supported by various animal studies. However, the contrary was observed in human studies, as albumin production was increased in chronically ill patients, leading to the hypothesis that a higher clearance rate leads to hypoalbuminemia in these patients. The exact pathophysiology of hypoalbuminemia is not entirely understood [36].

On the other hand, alkaline phosphatase is produced by various tissues such as the liver, the bile duct, kidney, and bone, making it a marker for cholestasis, bone turnover, and notably for tumor growth and metastasis [37,38].

Both laboratory markers can be altered in patients with a malignant tumor due to a tumor-induced pro-inflammatory state (albumin) and the direct effects of invasive tumor growth itself (alkaline phosphatase). Hence, combining both markers to form the AAPR has been shown to be a more accurate indicator of tumor behavior than albumin or alkaline phosphatase alone. A decrease in the ratio correlates significantly with an adverse effect on prognosis, including disease-free survival, progression-free survival, and cancer-specific survival [27].

In breast cancer, only three retrospective studies have evaluated the potential role of AAPR as an outcome predictor (Table 2) [27–29]. One of these assessed the role of AAPR as a predictor of response to NAC in the primary tumor, regardless of axillary involvement [27], while the others investigated AAPR as a predictor of overall survival [27–29]. These studies defined the AAPR cut-off value using a receiver operating characteristic curve (ROC curve) analysis to stratify patients into a low-AAPR group and a high-AAPR group (Table 2).

With a cut-off value of 0.583, AAPR has been shown to be a predictor of pCR in the primary tumor ($p = 0.007$, OR = 2.228, 95% CI 1.246–3.986) [27]. A nomogram for the prediction of the oncological outcome has been created based on four inflammatory-nutritional markers, including AAPR ($p = 0.043$ (HR = 0.447, 95% CI = 0.205–0.976) [28]. In a multivariate analysis, the AAPR has been demonstrated to be an independent variable affecting the overall survival in breast cancer patients ($p = 0.043$, HR = 0.447; 95% CI 0.205–0.976) [29].

In our study cohort, the AAPR threshold of 0.583 was applied based on the data reported by Qu et al. [27]. This is for two reasons: firstly, our sample was too small to conduct a ROC analysis, and secondly, the cut-off value proposed by Qu et al. [27] is more applicable to our cohort as it is the only study evaluating the role of AAPR in predicting tumor pCR as a primary endpoint in breast cancer, as opposed to overall survival.

Table 2. Overview of all studies investigating AAPR as a predictor for OS and/or pCR in breast cancer patients.

	Study Population	Study Design	AAPR Cut-Off	Cut-Off Definition	Primary Endpoint	Findings
Long et al., 2019 [29]	746	retrospective	0.525	ROC curve	OS	Low AAPR group: 5-year OS rate 80.16% High AAPR group: 5-year OS rate 92.66%
Qu et al., 2021 [27]	780	retrospective	0.583	ROC curve	T pCR	Univariate analysis: pCR correlated with AAPR ($p = 0.03$) Multivariate analysis: AAPR correlated with pCR ($p = 0.03$)
Hua et al., 2022 [28]	1259	retrospective	0.576	C-index and ROC curve	OS	Construction of INPS with Lasso Cox regression included NLR, MLR, PNI, and AAPR multivariate Cox regression: INPS independent indicator of OS (HR = 0.51; 95% CI: 0.35–0.75, $p < 0.001$)

This pilot study has some limitations to consider when interpreting the results. The small cohort leads to an increased risk of type II error, and this limitation meant that it was not possible to conduct a multivariate logistic regression analysis. For the same reason, we can assume that the sample size was not able to determine a significant result in the evaluation of primary tumor response. Additionally, the retrospective nature of this study may introduce more bias than prospective study methods.

On the other side, the strength of this study is that a statistically significant difference regarding nodal pCR has been found, despite the small sample.

The presented results provide a novel insight into the suitability of AAPR as a predictor for pCR in the axilla, an application that has not previously been investigated. Additionally, considering that pCR in axillary lymph nodes after NAC can be considered an early surrogate marker of the long-term outcome, ref. [39], the identification of pre-NAC predictors of axillary response can offer timely additional information on the oncological outcome. It means that in the future, a patient's laboratory phenotype, including inflammatory markers such as neutrophil-lymphocyte ratio and pan-immune-inflammatory value, could identify a population of newly diagnosed breast cancer patients with poor prognosis.

5. Conclusions

AAPR may represent a novel, easily applicable, and cost-effective predictor for axillary nodal pCR in cN+ breast cancer patients undergoing NAC. Further large prospective trials are required to validate this preliminary result and incorporate it into new predictive models and nomograms.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee Ticino, Switzerland (BASEC ID 2020-01121, approved 14 February 2023).

Informed Consent Statement: Eligible patients have been informed by a letter of non-objection and given the possibility to withdraw before data collection, according with protocol BASEC ID 2020-01121. Given the nature of the study (retrospective analysis), informed consent was not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author due to confidentiality issues bound by the ethics approval.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer. J. Clin.* **2018**, *68*, 394–424. [[CrossRef](#)] [[PubMed](#)]
2. Surveillance, Epidemiology, and End Results Program of the National Health Institute of the United States of America NIH National Cancer Institute Cancer Stat Facts: Female Breast Cancer. Available online: <https://seer.cancer.gov/statfacts/html/breast.html> (accessed on 20 March 2024).
3. Swisher, S.K.; Vila, J.; Tucker, S.L.; Bedrosian, I.; Shaitelman, S.F.; Litton, J.K.; Smith, B.D.; Caudle, A.S.; Kuerer, H.M.; Mittendorf, E.A. Locoregional Control According to Breast Cancer Subtype and Response to Neoadjuvant Chemotherapy in Breast Cancer Patients Undergoing Breast-conserving Therapy. *Ann. Surg. Oncol.* **2016**, *23*, 749–756. [[CrossRef](#)] [[PubMed](#)]
4. Jankowski, C.; Michel, E.; Vincent, L.; Beltjens, F.; Arnould, L.; Ladoire, S.; Coutant, C. Axillary pathologic response after neoadjuvant chemotherapy and surgery according to breast cancers subtypes and survival impact. *Bull. Cancer* **2023**, *110*, 605–615. [[CrossRef](#)] [[PubMed](#)]
5. Kuehn, T.; Bauerfeind, I.; Fehm, T.; Fleige, B.; Hausschild, M.; Helms, G.; Lebeau, A.; Liedtke, C.; von Minckwitz, G.; Nekljudova, V.; et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): A prospective, multicentre cohort study. *Lancet Oncol.* **2013**, *14*, 609–618. [[CrossRef](#)] [[PubMed](#)]
6. Boileau, J.; Poirier, B.; Basik, M.; Holloway, C.M.B.; Gaboury, L.; Sideris, L.; Meterissian, S.; Arnaout, A.; Brackstone, M.; McCready, D.R.; et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: The SN FNAC study. *J. Clin. Oncol.* **2015**, *33*, 258–264. [[CrossRef](#)] [[PubMed](#)]
7. Boughey, J.C.; Suman, V.J.; Mittendorf, E.A.; Ahrendt, G.M.; Wilke, L.G.; Taback, B.; Leitch, A.M.; Kuerer, H.M.; Bowling, M.; Flippo-Morton, T.S.; et al. Alliance for Clinical Trials in Oncology Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: The ACOSOG Z1071 (Alliance) clinical trial. *JAMA* **2013**, *310*, 1455–1461. [[CrossRef](#)]
8. Classe, J.; Loaec, C.; Gimbergues, P.; Alran, S.; de Lara, C.T.; Dupre, P.F.; Rouzier, R.; Faure, C.; Paillocher, N.; Chauvet, M.P.; et al. Sentinel lymph node biopsy without axillary lymphadenectomy after neoadjuvant chemotherapy is accurate and safe for selected patients: The GANEA 2 study. *Breast Cancer Res. Treat.* **2019**, *173*, 343–352. [[CrossRef](#)]
9. Wu, S.; Li, J.; Wang, Y.; Jin, K.; Yang, B.; Li, J.; Yu, X.; Mo, M.; Hu, N.; Shao, Z.; et al. Clinical feasibility and oncological safety of non-radioactive targeted axillary dissection after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: A prospective diagnostic and prognostic study. *Int. J. Surg.* **2023**, *109*, 1863–1870. Available online: https://journals.lww.com/international-journal-of-surgery/fulltext/2023/07000/clinical_feasibility_and_oncological_safety_of.4.aspx (accessed on 20 September 2024). [[CrossRef](#)]
10. Shen, J.; Gilcrease, M.Z.; Babiera, G.V.; Ross, M.I.; Meric-Bernstam, F.; Feig, B.W.; Kuerer, H.M.; Francis, A.; Ames, F.C.; Hunt, K.K. Feasibility and accuracy of sentinel lymph node biopsy after preoperative chemotherapy in breast cancer patients with documented axillary metastases. *Cancer* **2007**, *109*, 1255–1263. [[CrossRef](#)]
11. Alvarado, R.; Yi, M.; Le-Petross, H.; Gilcrease, M.; Mittendorf, E.A.; Bedrosian, I.; Hwang, R.F.; Caudle, A.S.; Babiera, G.V.; Akins, J.S.; et al. The role for sentinel lymph node dissection after neoadjuvant chemotherapy in patients who present with node-positive breast cancer. *Ann. Surg. Oncol.* **2012**, *19*, 3177–3184. [[CrossRef](#)]
12. Gradishar, W.J.; Moran, M.S.; Abraham, J.; Abramson, V.; Aft, R.; Agnese, D.; Allison, K.H.; Anderson, B.; Bailey, J.; Burstein, H.J.; et al. Breast Cancer, Version 3.2024, NCCN Clinical Practice Guidelines in Oncology. *J. Natl. Compr. Cancer Network* **2024**, *22*, 331–357. [[CrossRef](#)] [[PubMed](#)]
13. Tee, S.R.; Devane, L.A.; Evoy, D.; Rothwell, J.; Geraghty, J.; Prichard, R.S.; McDermott, E.W. Meta-analysis of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with initial biopsy-proven node-positive breast cancer. *Br. J. Surg.* **2018**, *105*, 1541–1552. [[CrossRef](#)] [[PubMed](#)]
14. Weber, W.P.; Matrai, Z.; Hayoz, S.; Tausch, C.; Henke, G.; Zimmermann, F.; Montagna, G.; Fitzal, F.; Gnant, M.; Ruhstaller, T.; et al. Association of Axillary Dissection with Systemic Therapy in Patients with Clinically Node-Positive Breast Cancer. *JAMA Surg.* **2023**, *158*, 1013–1021. [[CrossRef](#)] [[PubMed](#)]
15. Schipper, R.; de Bruijn, A.; van der Sangen, M.J.C.; Bloemen, J.G.; van den Hoven, I.; Schepers, E.E.M.; Vriens, B.E.P.; Boerman, T.; Rijkaart, D.C.; van de Winkel, L.M.H.; et al. Oncologic outcomes of de-escalating axillary treatment in clinically node-positive breast cancer patients treated with neoadjuvant systemic therapy—A two center cohort study. *Eur. J. Surg. Oncol.* **2024**, *50*, 108472. [[CrossRef](#)] [[PubMed](#)]
16. Gasparri, M.L.; de Boniface, J.; Poortmans, P.; Gentilini, O.D.; Kaidar-Person, O.; Banys-Paluchowski, M.; Di Micco, R.; Niinikoski, L.; Murawa, D.; Bonci, E.A.; et al. Axillary surgery after neoadjuvant therapy in initially node-positive breast cancer: International EUBREAST survey. *Br. J. Surg.* **2022**, *109*, 857–863. [[CrossRef](#)]

17. Ruf, F.; Kühn, T.; Hartmann, S.; de Boniface, J.; Gentilini, O.D.; Stickeler, E.; Cakmak, G.K.; Rubio, I.; Niinikoski, L.; Kontos, M.; et al. 120P AXSANA (AXillary Surgery After NeoAdjuvant Treatment) EUBREAST-3: An international prospective multicenter cohort study to evaluate different surgical methods of axillary staging in clinically node-positive breast cancer patients treated with neoadjuvant chemotherapy (NCT04373655). *Ann. Oncol.* **2022**, *33*, S178–S179. [[CrossRef](#)]
18. Corsi, F.; Albasini, S.; Sorrentino, L.; Armatura, G.; Carolla, C.; Chiappa, C.; Combi, F.; Curcio, A.; Della Valle, A.; Ferrari, G.; et al. Development of a novel nomogram-based online tool to predict axillary status after neoadjuvant chemotherapy in cN+ breast cancer: A multicentre study on 1,950 patients. *Breast* **2021**, *60*, 131–137. [[CrossRef](#)]
19. Kim, J.Y.; Park, H.S.; Kim, S.; Ryu, J.; Park, S.; Kim, S.I. Prognostic Nomogram for Prediction of Axillary Pathologic Complete Response After Neoadjuvant Chemotherapy in Cytologically Proven Node-Positive Breast Cancer. *Medicine* **2015**, *94*, e1720. [[CrossRef](#)]
20. Hwang, H.W.; Jung, H.; Hyeon, J.; Park, Y.H.; Ahn, J.S.; Im, Y.; Nam, S.J.; Kim, S.W.; Lee, J.E.; Yu, J.; et al. A nomogram to predict pathologic complete response (pCR) and the value of tumor-infiltrating lymphocytes (TILs) for prediction of response to neoadjuvant chemotherapy (NAC) in breast cancer patients. *Breast Cancer Res. Treat.* **2019**, *173*, 255–266. [[CrossRef](#)]
21. Zhang, P.; Song, X.; Sun, L.; Li, C.; Liu, X.; Bao, J.; Tian, Z.; Wang, X.; Yu, Z. A novel nomogram model of breast cancer-based imaging for predicting the status of axillary lymph nodes after neoadjuvant therapy. *Sci. Rep.* **2023**, *13*, 5952. [[CrossRef](#)]
22. Chen, P.; Zhao, T.; Bi, Z.; Zhang, Z.; Xie, L.; Liu, Y.; Song, X.; Song, X.; Wang, C.; Wang, Y. Laboratory indicators predict axillary nodal pathologic complete response after neoadjuvant therapy in breast cancer. *Future Oncol.* **2021**, *17*, 2449–2460. [[CrossRef](#)] [[PubMed](#)]
23. Cullinane, C.; Creavin, B.; O’Leary, D.P.; O’Sullivan, M.J.; Kelly, L.; Redmond, H.P.; Corrigan, M.A. Can the Neutrophil to Lymphocyte Ratio Predict Complete Pathologic Response to Neoadjuvant Breast Cancer Treatment? A Systematic Review and Meta-analysis. *Clin. Breast Cancer.* **2020**, *20*, e675–e681. [[CrossRef](#)] [[PubMed](#)]
24. Truffi, M.; Sottotetti, F.; Gafni, N.; Albasini, S.; Piccotti, F.; Morasso, C.; Tibollo, V.; Mocchi, M.; Zanella, V.; Corsi, F. Prognostic Potential of Immune Inflammatory Biomarkers in Breast Cancer Patients Treated with Neoadjuvant Chemotherapy. *Cancers* **2022**, *14*, 5287. [[CrossRef](#)] [[PubMed](#)]
25. von Au, A.; Shencoru, S.; Uhlmann, L.; Mayer, L.; Michel, L.; Wallwiener, M.; Hennigs, A.; Deutsch, T.; Riedel, F.; Heil, J.; et al. Predictive value of neutrophil-to-lymphocyte-ratio in neoadjuvant-treated patients with breast cancer. *Arch. Gynecol. Obstet.* **2023**, *307*, 1105–1113. [[CrossRef](#)] [[PubMed](#)]
26. An, L.; Yin, W.; Sun, D. Albumin-to-alkaline phosphatase ratio as a promising indicator of prognosis in human cancers: Is it possible? *BMC Cancer* **2021**, *21*, 247. [[CrossRef](#)]
27. Qu, F.; Li, Z.; Lai, S.; Zhong, X.; Fu, X.; Huang, X.; Li, Q.; Liu, S.; Li, H. Construction and Validation of a Serum Albumin-to-Alkaline Phosphatase Ratio-Based Nomogram for Predicting Pathological Complete Response in Breast Cancer. *Front. Oncol.* **2021**, *11*, 681905. Available online: <https://www.frontiersin.org/articles/10.3389/fonc.2021.681905> (accessed on 20 March 2024). [[CrossRef](#)]
28. Hua, X.; Duan, F.; Zhai, W.; Song, C.; Jiang, C.; Wang, L.; Huang, J.; Lin, H.; Yuan, Z. A Novel Inflammatory-Nutritional Prognostic Scoring System for Patients with Early-Stage Breast Cancer. *J. Inflamm. Res.* **2022**, *15*, 381–394. [[CrossRef](#)]
29. Long, Z.Q.; Hua, X.; Zhang, W.W.; Lv, S.W.; Deng, J.P.; Guo, L.; He, Z.Y.; Lin, H.X. Prognostic impact of the pretreatment albumin to alkaline phosphatase ratio for nonmetastatic breast cancer patients. *Cancer Manag. Res.* **2019**, *11*, 4809–4814. [[CrossRef](#)]
30. Schrenk, P.; Rieger, R.; Shamiyeh, A.; Wayand, W. Morbidity following sentinel lymph node biopsy versus axillary lymph node dissection for patients with breast carcinoma. *Cancer* **2000**, *88*, 608–614. [[CrossRef](#)]
31. Gasparri, M.L.; Kuehn, T.; Ruscito, I.; Zuber, V.; Di Micco, R.; Galiano, I.; Navarro Quinones, S.C.; Santurro, L.; Di Vittorio, F.; Meani, F.; et al. Fibrin Sealants and Axillary Lymphatic Morbidity: A Systematic Review and Meta-Analysis of 23 Clinical Randomized Trials. *Cancers* **2021**, *13*, 2056. [[CrossRef](#)]
32. McEvoy, M.P.; Feldman, S. Prevention and Treatment of Lymphedema in Breast Cancer. *Adv. Surg.* **2024**, *58*, 65–77. [[CrossRef](#)] [[PubMed](#)]
33. Lazar, A.M.; Mutuleanu, M.; Spiridon, P.M.; Bordea, C.I.; Suta, T.L.; Blidaru, A.; Gherghe, M. Feasibility of Sentinel Lymph Node Biopsy in Breast Cancer Patients with Axillary Conversion after Neoadjuvant Chemotherapy—A Single-Tertiary Centre Experience and Review of the Literature. *Diagnostics* **2023**, *13*, 3000. [[CrossRef](#)] [[PubMed](#)]
34. Gasparri, M.L.; Albasini, S.; Truffi, M.; Favilla, K.; Tagliaferri, B.; Piccotti, F.; Bossi, D.; Armatura, G.; Calcinotto, A.; Chiappa, C.; et al. Low neutrophil-to-lymphocyte ratio and pan-immune-inflammation-value predict nodal pathologic complete response in 1274 breast cancer patients treated with neoadjuvant chemotherapy: A multicenter analysis. *Ther. Adv. Med. Oncol.* **2023**, *15*, 17588359231193732. [[CrossRef](#)] [[PubMed](#)]
35. Eckart, A.; Struja, T.; Kutz, A.; Baumgartner, A.; Baumgartner, T.; Zurfluh, S.; Neeser, O.; Huber, A.; Stanga, Z.; Mueller, B.; et al. Relationship of Nutritional Status, Inflammation, and Serum Albumin Levels During Acute Illness: A Prospective Study. *Am. J. Med.* **2020**, *133*, 713–722. [[CrossRef](#)] [[PubMed](#)]
36. Soeters, P.B.; Wolfe, R.R.; Shenkin, A. Hypoalbuminemia: Pathogenesis and Clinical Significance. *J. Parenter. Enter. Nutr.* **2019**, *43*, 181–193. [[CrossRef](#)]
37. Jiang, C.; Hu, F.; Xia, X.; Guo, X. Prognostic value of alkaline phosphatase and bone-specific alkaline phosphatase in breast cancer: A systematic review and meta-analysis. *Int. J. Biol. Markers* **2023**, *38*, 25–36. [[CrossRef](#)]

38. Aminian, A.; Karimian, F.; Mirsharifi, R.; Alibakhshi, A.; Hasani, S.M.; Dashti, H.; Jahangiri, Y.; Ghaderi, H.; Meysamie, A. Correlation of serum alkaline phosphatase with clinicopathological characteristics of patients with oesophageal cancer. *East. Mediterr. Health J.* **2011**, *17*, 862–866. [[CrossRef](#)]
39. Chen, S.; Yu, C.; Chang, H.; Lin, Y.; Lo, Y.; Shen, S.; Kuo, W.; Tsai, H.; Chou, H.; Chu, C.; et al. Discrepancy of Breast and Axillary Pathologic Complete Response and Outcomes in Different Subtypes of Node-positive Breast Cancer after Neoadjuvant Chemotherapy. *J. Cancer* **2021**, *12*, 5365–5374. [[CrossRef](#)]

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