Editorial

Sarcopenia and monocyte-to-lymphocyte ratio as prognostic factors in early-stage breast cancer

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In the last decades, great research effort has been put on optimizing adjuvant treatments in patients with early-stage breast cancer (BC). Treatment optimization consists in therapy escalation—e.g., longer chemotherapy duration, use of additional cytotoxic agents in combination with/after standard anthracycline-taxane chemotherapy, use of dose-dense chemotherapy regimens—for patients at higher risk of disease relapse or death, and therapy de-escalation—e.g., shorter chemotherapy duration, avoiding the administration of anthracyclines or taxanes—for low-risk patients. To this aim, it is crucial to accurately predict the risk of disease relapse and patient death, thus modulating adjuvant treatments accordingly.

Clinical (e.g., patient age, ECOG PS) and tumor (e.g., pathologic T stage, N stage, hormone receptor status, HER2 expression, grading, ki-67) characteristics have been used in the last two-three decades to estimate the risk of BC relapse after curative surgery plus/minus adjuvant treatments, including chemotherapy, radiotherapy, endocrine therapy and trastuzumab (https://www.nccn.org). More recently, additional biological/clinical factors—e.g., the inability to achieve pathological complete response (pCR) after neoadjuvant chemotherapy in triple-negative BC (TNBC) and HER2-positive (HER2+) BC patients to predict benefit from adjuvant capecitabine (1) and T-DM1 (2), respectively—and gene expression profiles—e.g., the Oncotype DX panel to predict the usefulness of adjuvant chemotherapy in addition to endocrine therapies in patients with luminal BC (3) or the PAM50 panel to predict tumor sensitivity to trastuzumab in HER2+ BC (4)—have expanded our clinico-biological armamentarium to optimize the selection of the most appropriate adjuvant treatments after curative surgery for BC patients.

Despite these progresses, preclinical and clinical research is ongoing to identify new simple-to-measure and low-cost prognostic factors that are capable of improving the selection of patients candidate to receive different types of adjuvant therapies on the basis of their risk of tumor relapse after curative surgery. Among these factors, body composition and peripheral blood parameters that reflect systemic inflammation and immunity are emerging as potentially meaningful prognostic/predictive biomarkers.

The body mass index (BMI), as calculated as weight (in kilograms) divided by height in meters squared, is commonly used as an indirect indicator of excessive body fat content and altered body composition due to the simplicity of its assessment in the clinical practice. Of note, high BMI has been associated with worse survival in BC patients, with some exceptions (5-7). The main limitation of using the BMI as a prognostic parameter is that it does not faithfully reflect body composition, since it is unable to distinguish between lean and fat body mass. Indeed, it is becoming increasingly clear that not only fat mass, but also lean mass and the ratio between fat and lean mass are associated with

cancer patient prognosis (8). In particular, studies conducted in patients with advanced BC have shown that sarcopenia (low muscle mass) is associated with higher chemotherapy-induced toxicities and poorer clinical outcomes (9-11). In the context of advanced BC, the loss of skeletal muscle could simply reflect worse patient ECOG PS, thus identifying fragile patients that are at higher risk to develop treatment toxicities and complications; alternatively, sarcopenia could more specifically mirror a pro-inflammatory systemic state resulting from the secretion of pro-inflammatory cytokines by biologically aggressive cancer cells, which in turn directly or indirectly cause muscle breakdown and loss of lean mass. On the other hand, the impact of sarcopenia on the prognosis of patients with early-stage BC is more uncertain, and the available evidence is not univocal, with some studies indicating good prognostic role and other studies suggesting a detrimental effect (8,12,13).

Systemic inflammation and/or immunosuppression, which can be either the cause or the consequence of tumor development and progression, also play a key role in affecting tumor response to systemic treatments (14). Consequently, biomarkers reflecting systemic inflammation and immune system activation are being explored as prognostic factors in several clinical settings, especially in combination with other established patient or tumor-related variables. In recent years, composite measures derived from peripheral blood cell counts, which take into account both pro-inflammatory cells (i.e., neutrophils, monocytes, platelets) and antitumor immune cells (i.e., lymphocytes), have been investigated as potential prognostic/predictive factors of clinical outcome in cancer patients (15,16). Among these parameters are the neutrophil-to-lymphocyte ratio (NLR), the monocyte-to-lymphocyte ratio (MLR) and the platelet-to-lymphocyte ratio (PLR), which are easy-to-measure ratios of peripheral blood cell populations, and which reflect systemic inflammation/immune system activation more reliably than individual cell populations. Of note, high NLR, MLR and PLR have been associated with worse prognosis in patients with different types of malignancies and different disease stages (15). With regard to BC, a pooled meta-analysis of 15 studies, which included a total of 8,563 patients, found a significant association between high NLR and worse disease-free survival (DFS) or overall survival (OS) (16). Although this meta-analysis included patients with both early-stage and metastatic disease, 10 out of 15 studies only evaluated patients with early-stage BC (16). The available evidence on the bad prognostic role of the MLR in BC is also substantial (17-19). When compared to the NLR, which might be generically associated with systemic inflammation, the MLR could more reliably reflect a subgroup of immunosuppressive cells, including inflammatory monocytes and monocytic myeloid-derived suppressor cells (MDSCs) (20,21). It is still unclear if NLR and MLR have redundant prognostic/predictive roles, or if they are capable of providing independent prognostic information.

Deng *et al*. recently published the results of a retrospective study conducted in 97 Chinese female patients who underwent mastectomy for invasive stage II–III BC and lymph node metastases (22). Different BC subtypes were represented in this study: Luminal A- and B-like BC (64.9%), HER2+ BC (21.6%) and TNBC (13.4%). All patients received chemotherapy and radiotherapy after surgery. In this study, the authors collected information regarding patient clinical and laboratory parameters (including peripheral blood cell counts) and computed tomography (CT) image-based assessment of body composition prior to radiotherapy to investigate their association with clinical outcome, including DFS, relapse-free survival (RFS) and OS. The NLR, PLR and MLR were calculated from peripheral blood cell counts, while the skeletal muscle index (SMI) was calculated as muscle area at L3 (expressed in cm^2 at CT images) divided by height expressed in meters squared, and was used to define sarcopenia. Cut-off values for MLR, PLR, NLR and SMI were determined through ROC curve analysis.

This study showed a significant association between low SMI and better OS at both univariate and multivariable analysis [adjusted hazard ratio (aHR), 0.188; P=0.038], while there was no independent association between SMI and RFS or DFS. Similarly, high MLR was associated with significantly worse OS (aHR, 8.028; P=0.021) but not with RFS. Even more importantly, patients with both high SMI and high MLR (i.e., with high SMLR score) had remarkably poorer OS when compared to other patients, with an aHR of 13.272 (P=0.001), thus indicating that a combination of these factors can provide stronger prediction of clinical outcomes. The observed association between SMI, MLR or SMLR and patient OS (rather than RFS or DFS) suggests that these parameters might have a prognostic rather than predictive role.

The relationship between high MLR and worse patient prognosis in the study by Deng *et al*. is consistent with previous studies conducted in BC patients, and might reflect a higher proportion of peripheral blood immunosuppressive myeloid cells, such as MDSCs, which are typically found in

more aggressive and/or chemo-/radio-resistant neoplasms (17-19). On the other hand, Deng *et al*. found no significant association between NLR or PLR and clinical outcomes. Similar results emerged from the study by Goto *et al*., which was conducted in 239 early-stage TNBC patients treated with neoadjuvant chemotherapy followed by surgery, and in which high baseline MLR, but not NLR, was associated with clinical outcomes (23). The observed discrepancy between the prognostic role of MLR and NLR in many published studies suggests that these two parameters reflect different aspects of tumor biology and systemic inflammation/immunity, which may be also affected by patient and tumor characteristics, type of treatments administered and number of patients included in individual studies.

The findings by Deng *et al*. that sarcopenia is associated with significantly better OS and that the absence of sarcopenia (i.e., high SMI), coupled with high systemic inflammation (i.e., high MLR) provides the strongest prediction of worst clinical outcome, were quite surprising. Indeed, several studies correlated sarcopenia with poorer clinical outcomes in advanced BC patients (9,10); moreover, a recently published observational study conducted in 3,241 women with stage II–III BC showed that both sarcopenia and high body fat mass, as measured from CT scans through SMI and total adipose tissue area, respectively—were associated with worse OS (8). In this study, Caan *et al*. proposed that sarcopenia might reflect muscle breakdown resulting from high cancer aggressiveness and systemic inflammation (8). In our opinion, this explanation is not fully convincing in the context of early-stage BC, while it could be more credible in the setting of advanced disease, which is associated with significantly higher systemic inflammation, immunosuppression and risk of skeletal muscle breakdown (9,10).

Although the available evidence indicates a potentially detrimental impact of sarcopenia on the prognosis of patients with advanced BC, the role of low SMI and sarcopenia in early-stage BC is far from being fully clarified. For instance, in line with results of the study by Deng *et al*., Del Fabbro *et al*. found that sarcopenic early-stage BC patients treated with neoadjuvant chemotherapy are significantly more likely to achieve pCR and to have significantly longer OS when compared to non-sarcopenic patients (12). The authors of this study proposed that sarcopenic patients could be exposed to relatively higher concentrations of cytotoxic agents, since the presence of lower skeletal muscle mass is associated with increased concentrations of chemotherapeutic agents in the plasma, without necessarily implying higher treatment-related toxicity, since liver blood flow and drug catabolism are also augmented (24).

To reconcile the apparently contradictory results of different studies suggesting positive or negative impact of sarcopenia on early-stage BC patient prognosis, we hypothesize that the impact of sarcopenia on clinical outcomes could depend on specific clinical and tumor characteristics, including tumor type and stage (advanced *vs*. limited-stage; node-positive *vs*. node-negative disease), geographical origin of patients (e.g., the study here discussed involved only Asian patients), treatment regimens used as (neo)adjuvant therapies and the method used for defining sarcopenia (e.g., SMI threshold).

In conclusion, the paper by Deng *et al*. adds meaningful evidence about the interplay between lean mass content, systemic inflammation/immune system activation and OS in patients with lymph node-positive BC treated with surgery, radiotherapy and chemotherapy. Results of this study highlight the importance of studying the prognostic role of sarcopenia, especially in combination with parameters reflecting systemic inflammation and antitumor immunity, in BC patients with different disease stages and treated with different types of systemic therapies. In particular, the SMLR deserves further evaluation as a prognostic and/or predictive biomarker in larger and more selected populations of BC patients (i.e., patients with luminal-like BC, HER2+ BC or TNBC), and in different clinical contexts (i.e., early-stage *vs*. advanced BC). Integrating the SMLR into already used clinical and biological prognostic scores could contribute to improve the prediction of tumor relapse in early-stage BC patients, and to improve the choice of adjuvant therapies after curative surgery.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm.2020.03.171). The authors have no

conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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