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CANCER-ASSOCIATED ADIPOCYTES AND PROGNOSTIC VALUE OF PREOPERATIVE NEUTROPHIL-LYMPHOCYTE RATIO IN GASTRIC CANCER

Background. The neutrophil-to-lymphocyte ratio (NLR) turned out to be a routinely available marker capable to reflect the systemic inflammatory response created by a tumor. Gastric cancer (GC) grows in the anatomical vicinity of adipose tissue, which is also associated with low-grade inflammation. **Aim.** To investigate the usefulness of the combined use of preoperative NLR and density of intratumoral cancer-associated adipocytes (CAAs) for predicting the disease outcome in GC patients. **Materials and Methods.** A total of 151 patients with GC were eligible for retrospective analysis between 2009 and 2015. NLR preoperative values were calculated. Perilipin expression in tumor tissue was examined immunohistochemically. **Results.** Low preoperative NLR is the most reliable prognostic factor for the favorable outcome for patients with low density of intratumoral CAAs. Patients with a high density of CCAs are at high risk of lethal outcomes independently of the value of preoperative NLR. **Conclusion.** The results have clearly shown an association between preoperative NLR and the density of CAAs in the primary tumor of GC patients. The prognostic value of NLR is essentially modified by means of the individual density of intratumoral CAAs in GC patients. The elevated NLR could be of significant predictive potential for a negative prognosis for patients with tumors characterized by the high density of CAAs independently of BMI.

Keywords: gastric cancer, prognostic value of NLR, BMI, cancer-associated adipocytes.

Chronic inflammation representing an aberrantly prolonged form of a protective response to a loss of tissue homeostasis is involved in carcinogenesis and can promote tumor growth, invasion, angiogenesis, and metastasis. As a result, many cancers are inflammation-related. There is

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increasing and consistent evidence that inflammatory status is associated with prognosis and correlates with poor survival in various cancers [1, 2].

Different biomarkers of systemic inflammation have been examined over the past decade in an attempt to refine the stratification of patients to treatment and predict survival. Some of them, namely neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) have been recognized as promising prognostic factors for improving predictive accuracy and were introduced into clinical practice for risk-rating in cancer patient treatment. Clinicians need to consider patients with elevated ratios for decisions on immunotherapy strategy [3].

Neutrophils are traditionally considered as inflammatory immune cells, and in recent years, they have attracted increasing attention because of their cancer-promoting effects [4]. High levels of neutrophils are closely associated with disease progression and poor clinical outcomes. NLR turned out to be a routinely available marker, which can reflect the status of systematic inflammation response [5—8]. NLR has been proven to affect the prognosis for several types of cancer, in particular, in patients with small-cell lung cancer and non-small-cell lung cancer [9], esophageal squamous cell carcinoma [10], ovarian cancer [7, 11], colorectal cancer [12], gallbladder carcinoma [13, 14], and renal cell carcinoma [8].

The obesity is one of the major problems of public healthcare in the XXI century. Starting from the 1980s, the incidence of obesity in many European countries increased threefold and continues to increase sharply. Besides decreased physical capability and psychological problems, excess weight increases the risk of many diseases including cardiovascular pathology, diabetes, and cancer [15, 16]. The risk of cancer in obese people increases, and the course of the disease in cancer patients with excess weight deteriorated significantly. Nevertheless, some other factors such as the obesity type and pattern, sex-and-age distribution of patients, tumor localization, smoking habits, menopause, treatment regime, and hormonal therapy should be also taken into account [17, 18]. The fat depots of different localization (e.g., subcutaneous and visceral) differ in their cell content and endocrine function and, therefore, in their effects on the organs and tissues of the body. In particular, cancer-associated adipocytes (CAA) originating from the visceral adipose tissue surrounding tumor are the source of the energy and adipokines required for tumor progression [19, 20]. Furthermore, according to the current concept, body mass index (BMI) as an indicator of obesity grade is not sufficiently correct, and in clinical practice, it should be used with certain caution [21, 22]. Therefore, the study of obesity in oncological clinics requires both the assessment of the adipose tissue state and the evaluation of its negative effects on the functions of organs and tissues. The in-depth study of the obesity-associated factors of tumor microenvironment seems to be advantageous for delineating them as markers of the disease course in obese cancer patients [23]. Gastric cancer (GC) belongs to the tumors originating and progressing at the sites of the natural accumulation of adipose tissue acquiring the features of chronic inflammation and metabolic disbalance [24, 25].

The aim of this study was to investigate whether there is a relationship between the prognostic value of preoperative NLR and the density of CAAs in the primary tumor of GC patients.

Materials and Methods

Patients. A total of 151 patients (95 men and 56 women) with primary Gc treated in the Kyiv Clinical Oncological Center were eligible for retrospective analysis between 12.11.2009 and 01.03.2015. No patients received any pre-operative anticancer therapy. Tumors were classified and staged according to the 2002 version of the UICC staging system [26]. Histological types of

tumors were evaluated by the WHO histological classification (2000) [27].

The preoperative NLR in all patients was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count in the peripheral blood.

Immunohistochemical analysis of perilipin expression in tumor tissue. Expression of perilipin ($Plin5^+$) as a marker for viable adipocytes was analyzed on deparaffinized slides using specific polyclonal rabbit antibodies (Perilipin-5/OXPAT antibody, Termoscientific, USA) at a 1:200 dilution. Immunoreactions were detected and visualized by the polymer–peroxidase method (EnVision+/HRP and 3,3-diaminobenzidine (DAB); DakoCytomation, Denmark) followed by counterstaining with Mayer hematoxylin. Immunopositive cells were counted per 1000 cells in each slide, and the number of positive cells was reported in percent.

Body mass index (BMI, kg m^{-2}). Patients were classified according to BMI, following the WHO definitions, as a normal weight (BMI < 25.0 kg/m^2) or overweight (including obesity) (BMI > 25.0 kg/m^2).

Statistical analysis. All statistical analyses were conducted using the NCSS 2000/PASS 2000 and Prism, version 4.03 software packages. The survival rates were assessed using the Kaplan — Meier method, and differences in survival were analyzed with the log-rank test. Prognostic values of relevant variables were analyzed by means of the Cox proportional hazards model using hazard ratio (HR) and χ^2 test. Two-tailed p values < 0.05 were considered to indicate a statistically significant difference.

Results

Individual patient data from a total 151 histologically confirmed GC cases were included in this study. The cut-off value for preoperative NLR was 2.75 (range 0.9—12.9), and all GC patients have been assigned to high and low groups according to the cut-off values for NLR and according to BMI: at normal weight (BMI < 25 kg/m^2) and overweight including obesity (BMI > 25 kg/m^2).

Overall, the number of patients with NLR < 2.75 and NLR >2.75 was 47.6% and 52.4%, respectively. Patients with NLR >2.75 had a significantly poorer prognosis than those with NLR <2.75: overall, 40.9% and 57.8% patients with NLR < 2.75 and with NLR >2.75, respectively, died; and their death was related to GC.

Median follow-up time was 22.9 (range 7.7—71.4) and 18.9 (range 5.5—52.47) months from diagnosis for patients with low and high NLR, respectively. Survival of GC patients was assessed by Kaplan — Meier method in accordance with preoperative NLR (Fig. 1). High preoperative NLR was associated with unfavorable outcomes and shorter OS compared to patients with low NLR (HR 2.14, 95% CI 1.142—4.007, $\chi^2 = 5.047$, $p = 0.0247$), which is consistent with literature data confirming the prognostic value of preoperative NLR in GC patients.

Nevertheless, the survival as well as risk of fatal outcome did not differ significantly in patients with low and high NLR whether their BMI was <25 or >25 ($p > 0.05$) (Table 1).

In our previous works, we have shown that the high density of CAAs in tumors of patients with

Table 1. **Survival of GC patients differing in BMI and prognostic NLR values**

Indices	Patients with BMI <25		Patients with BMI >25	
	Low NLR	High NLR	Low NLR	High NLR
Lethal outcomes (%)	43.7	54.2	33.3	45.0
Median follow-up time, (range, months)	19.5 (3.6—48.2)	18.2 (4.1—32.7)	22.6 (7.2—71.4)	24.1 (12.4—50.5)

BMI > 25 increased by a factor of 11 (OR 11.01, χ^2 =12.9, 95% CI 28.933—5.749, $p < 0.01$) as compared with BMI < 25. Almost 45.0% of patients with normal weight had a high density of CAAs in tumors as compared to 88.5% patients with GC and obesity ($p < 0.001$). Since the median content of CAAs in tumors was 26.5%, we took this value as the cut-off in our present study and classified all cases into high- or low- CAA density groups [28, 29].

We have studied the survival indices of GC patients with high and low NLR depending on the density of CAAs in the primary tumor (Table 2).

These data allow us to suggest that prognosis of disease outcome by means of preoperative low NLR for GC patients is the most favorable when tumors are characterized by low density of CAAs: OS of patients is longer with lower risk of lethal outcome compared to patients with high NLR who have unfavorable outcome ($p < 0.05$). When the density of CAAs is high, the median follow-up time does not change significantly depending on NLR values but the risk of lethal outcome is significantly high as compared to patients with the low density of CAAs ($p < 0.05$).

The survival of GC patients with high and low BMI depending on NLR and CAAs density was further analyzed (Table 3).

The most favorable prognosis by means of preoperative low NLR for disease outcome remains for patients with both normal weight and overweight, when their tumors are characterized by low density of CAAs ($p < 0.05$). The most disturbing situation is for patients with normal weight, low intratumoral CAA density, and elevated NLR: they have a shorter survival time and 18% risk of lethal outcome as compared to overweighed patients. This conclusion coincides with earlier obtained data showing that the OS of patients with BMI < 25 is sig-

Table 2. **Survival of GC patients with high and low NLR depending on the density of CAAs**

Indices	Patients with low NLR		Patients with high NLR	
	Density of CAAs			
	low	high	low	high
Lethal outcomes (%)	8.7	64.7	13.3	71.4
Median follow-up time, (range, months)	28.7 (9.3—71.4)	21.5 (7.2—32.5)	16.2 (4.6—41.8)	20.9 (8.1—51.2)

Table 3. **Survival of GC patients with high and low BMI depending on NLR and density of CAAs**

Indices	BMI < 25				BMI > 25			
	Density of CAAs				Density of CAAs			
	low		high		low		high	
	Preoperative NLR				Preoperative NLR			
	low	high	low	high	low	high	low	high
Lethal outcomes (%)	9.1	18.2	75.1	84.6	0	0	53.3	60
Median follow-up time, (range, months)	29.7 (14.9—48.3)	19.9 (3.9—41.6)	14.4 (10.8—21.1)	19.4 (2.1—37.1)	44.6 (15.2—71.4)	22.2 (12.4—50.5)	27.5 (7.2—36.9)	22.5 (5.5—51.5)

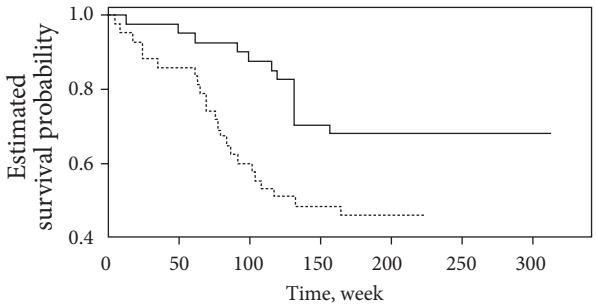

Fig. 1. Kaplan-Meier OS curves for all GC patients as a function of preoperative prognostic value of NLR (solid line — NLR < 2.75; dotted line — NLR > 2.75), log-rank test, $\chi^2 = 5.047$, $p = 0.0247$

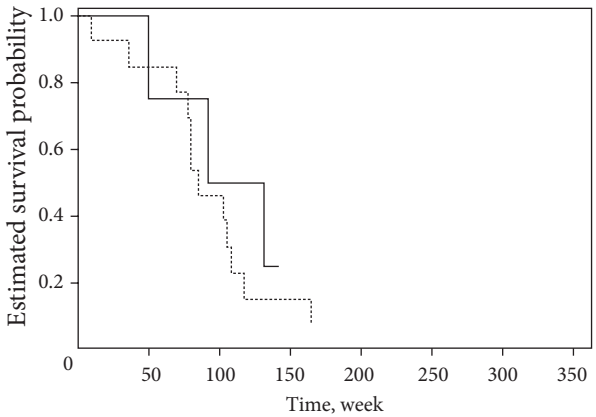

Fig. 2. Kaplan-Meier OS curves for GC patients (BMI < 25) as a function of preoperative prognostic value of NLR (solid line — NLR < 2.75; dotted line — NLR > 2.75), log-rank test, $\chi^2 = 1.74$, $p > 0.547$. All patients had high intratumoral density of CAAs

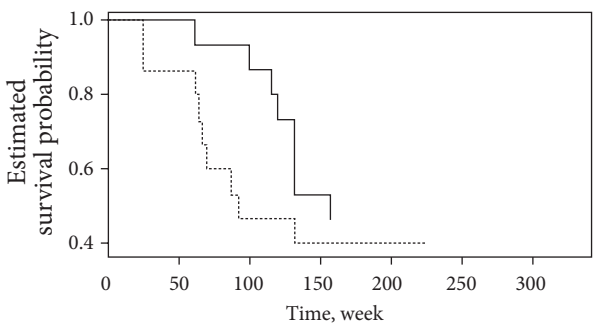

Fig. 3. Kaplan-Meier OS curves for GC patients (BMI > 25) as a function of preoperative prognostic value of NLR (solid line — NLR < 2.75; dotted line — NLR > 2.75), log-rank test, $\chi^2 = 2.09$, $p > 0.668$. All patients had high intratumoral density of CAAs

nificantly poorer compared to patients with BMI > 25 ($p = 0.006$) [30].

Low preoperative NLR cannot ensure a reliable prognosis for patients having high intratumoral CCAs density in both BMI groups: they are at high risk of lethal outcome.

Patients with the high density of CCAs are at high risk of lethal outcome independently of the value of preoperative NLR. The Kaplan — Meier survival analysis demonstrated the absence of differences between the survival of patients who have high intratumoral CAAs density and different values of preoperative NLR (low or high) for patients with normal weight (Fig. 2) and overweight (Fig. 3), which is in accordance with the results presented in Table 3.

Therefore, the elevated NLR is a significant predictive potential for a negative prognosis for patients with tumors characterized by the high density of CAAs independently of BMI.

Discussion

Advanced GC has a poor prognosis because of metastasis. Thus, there is a need for a reliable indicator for prognosis and improving therapeutic strategies. The meta-analysis reveals that preoperative NLR proved to be a useful predictor of postoperative survival of patients with early GC stages, that is, stages I—II, and lymph node metastasis. Also, the peritoneal cancer index is useful in prognosis for patients with peritoneal metastasis of GC [8, 31—36].

It has been shown that preoperative NLR correlates not only with different disease stages but also with the response to chemotherapy. Patients with lower NLR have a significantly better complete response to chemotherapy *vs.* those with a higher NLR ($p < 0.001$). NLR can be used as a significant prognostic biomarker in metastatic GC patients receiving palliative chemotherapy [6, 31, 37].

The correlative studies (15 studies, >8500 patients) originated from ten different countries,

in particular, UK, Japan, and China, have shown that NLR is elevated in patients with more advanced or aggressive disease evidenced by increased tumor stage, nodal status, and the number of metastatic lesions [38].

However, there are doubts concerning the prognostic value of preoperative NLR: in patients with small-cell lung cancer, it remains controversial; in patients with esophageal cancer, it is unclear [39—41]. Jin et al. [42] have reported that logistic regression model analyses revealed that the combination of NLR_high/PLR_high was an independent prognostic factor in breast cancer patients but there was no significant difference in NLR analyzed separately. Dupré et al. [43] have noticed that elevated NLR seems to be associated with decreased survival, but the studies of this marker are very heterogeneous. The main limitation is the variety of thresholds used to dichotomize patients, so that reproducibility and reliability of leukocytes-based scores can be questioned. Hence, there is no sufficient evidence to support the use of them in clinical practice.

This led researchers to look for other more reliable independent prognostic indices such as a preoperative platelet-to-albumin ratio in patients after pancreatic resection with curative intent [44], preoperative systemic inflammation score (SIS) based on the preoperative serum albumin level, lymphocyte-to-monocyte ratio in patients with resectable GC [45], as well as the combined index of hemoglobin, albumin, lymphocyte, and platelet (HALP) as a novel marker to reflect systemic inflammation in patients with pancreatic cancer, GC, colorectal cancer, and small-cell lung cancer [46—49].

Unfortunately, biologic mechanisms underlying the prognostic value of preoperative ratios remain incompletely understood.

Current data generally indicate the influence of excess weight on the course of GC, in particular, in colorectal cancer and cancers of the esophagus, stomach, pancreas, and liver. The results of these studies contain contradictions and are debatable. The relationship between BMI and the disease course in patients with gastrointestinal tract cancer definitely exists but it is not linear. Indicators such as the distribution of adipose tissue (ratio of visceral and subcutaneous fat volumes), which significantly increase the prognosis effectiveness, are proposed to be used in addition to BMI. Researchers believe that the impact of adipose tissue dysfunction (energy imbalance, inflammation, sex hormone metabolism) on both the tumor microenvironment and homeostasis of other tissues and organs is an underestimated but extremely important risk factor for the occurrence and course of cancer, in particular, gastrointestinal tract cancer [50—53].

Solid tumor growth and metastasis require the interaction of tumor cells with the surrounding tissues. Due to the ubiquitous nature of adipose tissue, many types of solid tumors grow in proximate or direct contact with adipocytes and adipose-associated stromal and vascular components [54] such as fibroblasts and other connective tissue cells, stem and progenitor cells, endothelial cells, cells of innate and adaptive immunity, and extracellular signaling and matrix components. Adipocytes modulate the tumor microenvironment by promoting angiogenesis, affecting immune cells and altering metabolism to support the growth and survival of metastatic cancer cells [55]. Pathophysiological studies provide conclusive evidence of a strong link between obesity and GC course taking into account that GC grows in the anatomical vicinity of adipose tissue and adipocytes are predominant in tumor microenvironment [56].

Adipocytes are typically absent within the normal parenchyma of epithelial glands. However, O'Sullivan et al. [57] suppose that in invasive carcinomas, adipocytes come in direct contact with tumors, especially in the reproductive (prostate, uterus, breast) and digestive organs. A considerable number of patients with advanced epithelial cancers (gastric, colon, serous en-

dometrial, and ovarian) have a clear predilection for metastasis to the great omentum, an organ that consists mainly of adipose tissue. Such preferential spread of tumor cells remains unclear. The results of the study by Xiang et al. [58] demonstrate that adipocytes may serve as the exogenous source of oleic acid, which promotes GC cell invasion through the PI3K/Akt signaling pathway.

Adipose tissue is a complex dynamic organ with whole-body immune and metabolic influences that can regulate bodily homeostasis, systemic metabolism, inflammation, and tumor behavior [59, 60]. Excessive adipose expansion during obesity development causes adipose dysfunction and inflammation leading to the increase in the systemic proinflammatory factor levels. Recent studies suggest that adipocytes are a potent source of pro-inflammatory cytokines. Cells from adipose tissue enter the cancer microenvironment and enhance protumoral effects [61, 62].

Interacting with cancer cells, adipocytes dedifferentiate into pre-adipocytes or are reprogrammed into CAAs [56]. A key role in this mechanism seems to be played by the onset of low-grade systemic inflammation, which highlights the importance of the interplay between adipocytes and immune system cells [56, 62]. Excessive adipose expansion causes adipose dysfunction and inflammation increasing systemic levels of proinflammatory factors [63].

Thus, based on the literature data, it can be assumed that inflammatory processes, characteristic of adipose tissue dysfunction, change the parameters of patients' peripheral blood. Therefore, the combination of NLR and CAAs indices for predicting the course of gastrointestinal tract cancer, in particular GC, is expedient. To the best of our knowledge, currently there are no such findings in the available literature.

The obtained results clearly show that there is association between preoperative NLR and the density of CAAs in primary tumor of GC patients, which is very complicated. Prognosis by the value of preoperative NLR is essentially modified by the density of CAAs in primary tumor, indicating the expediency of the evaluation of intratumoral CAAs density.

In conclusion, NLR in GC patients could be a factor of the unfavorable course of the disease and high risk of death accounting the CAAs density independently of BMI. Our results confirm that the dysfunctional state of adipose tissue rather than BMI affects the tumor microenvironment enhancing its aggressiveness and aggravating the course of the disease. Therefore, the use of the accepted markers of GC course, in particular NLR in combination with CAAs would be advantageous for improving prognosis of the disease outcome and personalized correction of treatment regimens allowing for the prolongation of patient survival.

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ПУХЛИНОАСОЦІЙОВАНІ АДИПОЦИТИ І ПРОГНОСТИЧНЕ ЗНАЧЕННЯ СПІВВІДНОШЕННЯ НЕЙТРОФІЛІВ ДО ЛІМФОЦИТІВ У ХВОРИХ НА РАК ШЛУНКА

Стан питання. Відомо, що передопераційне співвідношення нейтрофілів до лімфоцитів (НЛС) є стандартним доступним маркером, здатним відображати системну запальну відповідь, спричинену пухлиною. Рак шлунка (РШ) анатомічно розташований в оточенні жирової тканини, яка також характеризується хронічним запаленням. **Метою** цього дослідження було вивчити прогностичне значення спільного застосування передопераційного НЛС та щільності пухлино-асоційованих адипоцитів для прогнозування перебігу РШ. **Матеріали та методи.** Проведено ретроспективний аналіз даних 151 пацієнта із РШ (між 2009 та 2015 роками). НЛС обчислювалося виходячи з абсолютних значень в периферичній крові і проводилося імуногісто-

хімічне визначення експресії периліпіну в пухлинній тканині. **Результати.** Низьке прогностичне значення НЛС є найбільш ефективним показником сприятливого перебігу захворювання для пацієнтів, які мають низьку щільність пухлино-асоційованих адипоцитів (ПАА) в пухлині. Для пацієнтів з високою щільністю ПАА ризик несприятливого прогнозу є високим, незалежно від передопераційних значень НЛС. **Висновок.** Отримані результати чітко показують, що існує взаємозв'язок між передопераційним прогностичним значенням НЛС і щільністю ПАА в первинній пухлині хворих на РШ. Прогноз перебігу захворювання за значенням НЛС суттєво модифікується індивідуальною щільністю ПАА в пухлинах хворих на РШ і, можливо, тому при самостійному використанні не завжди виправдовує свою цінність щодо реального прогнозу. Показник щільності ПАА в пухлині надасть можливість застосовувати передопераційне значення НЛС в якості корисного біомаркера для найточнішого персоналізованого прогнозу післяопераційної виживаності хворих на РШ.

Ключові слова: рак шлунка, прогностичне значення співвідношення нейтрофілів до лімфоцитів, ІМТ, пухлино-асоційовані адипоцити