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Neutrophil to lymphocyte ratio as a prognostic marker for advanced stage ovarian cancer

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ABSTRACT

Ovarian cancer remains one of the most aggressive malignancies which is frequently diagnosed in advanced stages of the disease, when disseminated lesions are already present. In order to maximize the rates of complete debulking surgery, different prognostic markers have been investigated. The aim of the current paper is to investigate the prognostic value of neutrophil to lymphocyte ratio in advanced stage ovarian cancer patients submitted to debulking surgery.

Keywords: ovarian cancer, neutrophil to lymphocyte ratio, prognostic, complications

INTRODUCTION

Despite significant advantages reported in the field of surgical and medical oncology, ovarian cancer still remains a silent killer, being responsible for a significant number of deaths worldwide especially due to the fact that there is no screening test which could provide a more rapid diagnostic of this disease [1-3]. Although for a long period of time CA125 has been considered as a golden standard in identifying ovarian cancer patients, it has the disadvantage that a normal value could not exclude the presence of an early stage disease or a non-secretory ovarian tumor in any stage of the disease [4].

In the meantime, progress has been made in regard to the understanding of the complex relation ship between inflammation and tumorigenesis; therefore, it has been widely demonstrated that the presence of a proinflammatory status, translated through the presence of a higher number of neutrophils or platelets and a low number of lymphocytes is usually correlated not only with a proinflammatory condition but also with a favorable environment for tumor development [5,6]. Moreover, it has been widely demonstrated the fact that the presence of a high neutrophil to lymphocyte ratio (NLR) is usually associated with the presence of obesity, of metabolic

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syndrome and with smoking habits; meanwhile, loosing weight, reducing the metabolic syndrome and smoking cessation leads to the decrease of NLR demonstrating therefore the reversibility of this condition [7,8]. The well-known correlation ships between inflammation, obesity, metabolic syndrome, smoking habits and tumorigenesis in association with the relationships between these parameters and NLR enabled the investigators worldwide to consider that NLR could serve as a new prognostic marker for different malignancies. Moreover, when it comes to ovarian cancer, it has been stipulated the fact that CA125 has the ability to bind to certain subgroups of leukocytes and therefore, a more complex relationship between the CA125 level and white blood count has been imagined [9]. The aim of the current paper is to investigate the correlation ship between preoperative NLR and the overall outcomes of advanced stage ovarian cancer.

MATERIAL AND METHODS

After receiving the approval of the Ethics Committee no 61/2023 data of patients submitted to surgery for advanced stage ovarian cancer were in Cantacuzino Clinical Hospital between 2017 and 2020 were retrospectively reviewed. Finally 38 cases were identified and were further included in the current paper.

RESULTS

The optimal cut-off value was set at 4 by the receiver operating characteristic (ROC) to distinct the one year survival outcomes; this value was associated with a sensitivity of 745, a specificity of 85%, a positive predictive value of 56,8% and a negative predictive value of 89,4% for early postoperative mortality.

According to this parameter, patients were classified into two groups: cases with NLR<4 – 21 cases and NLR>4 – 17 cases.

When studying the demographic and clinical characteristics, we observed that patients with NLR > 4 were older, presented a poorer ECOG performance index, a poorer ASA score and more severe clinical symptoms when compared to cases with NLR < 4.

Demographic and clinical characteristics of the two subgroups are presented in Table 1.

When it comes to the perioperative and postoperative status, analysis of the two subgroups revealed the fact that patients included in the first category were more likely to be submitted more often to complete debulking surgery when compared to the second group and necessitated less extended resections. As expected, cases in the first group developed less postoperative complications and necessitated shorter hospital in stay when compared to patients in the second group; meanwhile, patients in the first subgroup reported a 30 days postoperative morbidity rate of 23% and a 30 day mortality rate of 1%, significantly lower than cases in the second group, in which the morbidity rate was of 56% and the 30 day mortality rate was of 5%.

TABLE 1. Demographic and clinical characteristics of the two subgroups

Parameter	NLR<4 – 21 cases	NLR>4 – 17 cases	P value
Age (years, mean)	51 (38-63)	60 (45-76)	0.53
ECOG performance: 0 1 2	 13 5 3	 7 7 3	0.02
ASA score I II III IV	 9 6 4 3	 3 3 6 5	0.01
Clinical symptoms - None - Mild - Severe	 10 7 4	 3 3 11	0.003

As for the long term outcomes, patients in the first group reported a progression free survival rate of 11 months and an overall survival rate of 23 months while those in the second group reported a progression free survival of 6 months and an overall survival rate of 17 months.

DISCUSSIONS

The correlation ship between NLR and malignancy has been widely explored in different malignancies and proved to be a significant tool in order to better identify cases with more aggressive tumoral behavior. The presence of an increased number of neutrophils is usually associated with the presence of high amounts of cytokines, interleukins and tumor growth factors which will further create a proper environment for tumoral transformation of the cells, tumoral progression and in the meantime tumoral spread; meanwhile the presence of a higher number of lymphocytes is usually considered to be a good prognostic factor, lymphocytic peritumoral infiltration being usually associated with improved outcomes [10-12]. In this respect, it is easily to be understood the fact that a lower NLR is usually considered to be a favorable prognostic factor in the setting of different malignancies.

When it comes to ovarian cancer, few studies have been conducted on this issue; however, pre-

liminary results came to demonstrate that the value of this parameter can identify CA125 negative ovarian cancer cases and to predict the long term outcomes [13,14]. In this respect, Cho et al demonstrated that up to 37% of cases diagnosed with ovarian cancer and normal levels of CA125 have a higher level of NLR [15].

When it comes to the correlation ship between the preoperative NLR value and the outcomes of ovarian cancer patients, the study conducted by Wang et al. and published in 2015 came to demonstrate that higher preoperative NLR values were significantly associated with advanced FIGO stage, poorly differentiated tumors, increased serum levels of CA125, higher risk of lymph node metastases and poorer progression free and respectively overall survival rates. These results were particularly significant in cases presenting a NLR value higher than 2,65, value which was also associated with a poorer rate of chemotherapeutical response [16]. Another interesting paper was published by Komura in 2017; in this paper the authors investigated the influence of preoperative neutrophil count and respectively the influence of the preoperative NLR on the long term outcomes of epithelial ovarian cancer. Cut of values of 8000/microl and respectively 4 were established for the absolute number of neutrophils and respectively for the NLR; the authors demonstrated that patients presenting higher values when compared to the ones established as cut off values for neutrophils and respectively NLR reported a significantly poorer outcome in terms of progression free and respectively overall survival rates. Moreover the authors divided the patients into four groups: high risk group – presenting elevated NLR and elevated neutrophil count, intermediate risk – presenting elevated NLR with normal neutrophil count and respectively low risk – presenting low NLR and respectively low number of circulating neutrophils and demonstrated the fact that this classification allows a more personalized, tailored treatment for ovarian cancer patients [17].

An interesting meta-analysis conducted on the issue of NLR prognostic of survival in different gynecological cancers which included 26 studies and 10530 patients came to demonstrate that when it comes to ovarian cancer a higher than the cut off value of NLR was usually associated with a poorer overall survival and event free survival [14].

Moreover, the preoperative NLR value seem to be an important tool in order to distinguish patients who could benefit most from the administration of neoadjuvant chemotherapy when compared to per primam debulking surgery. Therefore, according to Tal et al. patients with higher NLR should be rather submitted to neoadjuvant chemotherapy while cases with lower values might benefit most from per primam debulking surgery [18].

Interestingly, it seems that the pretreatment NLR value is also efficient in order to predict the long term outcomes in platinum sensitive cases, a cut off value of 3 being taken into account; however, according to Farolfi et al., this predictive value of NLR is lost in cases in which bevacizumab is added in the setting of the adjuvant therapy [19]. A more recent study conducted by Perez Fidalgo et al. and published in 2021 came to underline the fact that the NLR value has a predictive value for platinum resistant cases too; therefore, the authors underlined the fact that both in univariate and multivariate analysis a lower NLR value was associated with improved outcomes after pegylated liposomal doxorubicin administration in association with Olaparib, the cut off value in this study being established at 2 [20].

Recently, a study originating from Taiwan came to underline the fact that the preoperative NLR value has a significant predictive value in order to identify cases at risk for early mortality after cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy; the study included 132 such patients submitted to this procedure, while the cut off value of NLR was established at 4,4; among these cases the most commonly encountered type of malignancy was represented by ovarian cancer, which was encountered in 60 cases. A higher NLR value at the time of the initial diagnosis was significantly associated with a higher value of the peritoneal carcinomatosis index, with incomplete cytoreduction and poor degree of tumoral differentiation. Meanwhile, patients with a higher NLR value proved to have a higher risk for delayed extubation, for intensive care unit readmission, for major perioperative complications and for early mortality. Moreover, they reported a significantly lower rate of overall survival. The authors went even further and also analyzed the early postoperative NLR values; according to the preoperative and postoperative NLR values, they classified patients in four categories: cases presenting high preoperative and respectively postoperative NLR values, cases presenting lower preoperative and postoperative value, cases presenting higher preoperative and lower postoperative values and cases presenting lower preoperative and respectively higher postoperative values of NLR when compared to the cut off value of 4,4. As expected, the best outcomes were reported among patients with lower preoperative and postoperative NLR values (reported to the established cut off value) while the worst prognosis was reported in cases presenting higher preoperative and respectively postoperative NLR values; interestingly there was no significant difference between cases presenting a lower preoperative and higher postoperative value and respectively a higher preoperative and lower postoperative value of NLR. In multivariate analy-

sis, factors associated with poorer outcomes were represented by incomplete debulking surgery, major postoperative complications, higher than 4,4 preoperative NLR value and respectively NLR change other than low preoperative-low postoperative NLR values. Furthermore, they built a scoring system which took into consideration all the four mentioned factors and created a scale of 0 to 16 points; according to this scale they classified the patients into four categories: 0-2 points, 3-7 points, 8-10 points and respectively 11-16 points and demonstrated that the mean overall survival rates were 33,3+/-2,3 months for the first class, 28,1+/-2,8 months for the second class, 18+/-3,7 months for the third class and respectively 4,2+/-0,8 months for the fourth class creating therefore a new predictive model which should be able to better identify cases who seem to benefit most from this aggressive surgical approach [21].

CONCLUSIONS

Neutrophil to lymphocyte ratio represents a promising prognostic marker in order to identify patients with ovarian cancer and poor biology and who should be rather candidates for neoadjuvant therapies than for debulking surgery in order to improve the long term outcomes and to increase the chances to achieve long term survival rates.

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