ORIGINAL RESEARCH

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Preoperative neutrophil/lymphocyte ratio as prognostic factor in epitelial ovarian cancer

Cociente neutrófilos/linfocitos preoperatorio como factor pronóstico en el cáncer epitelial de ovario

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ABSTRACT

Objectives: To determine if there is an association between the neutrophil to lymphocyte ratio (NLR) and prognosis in patients with epithelial ovarian cancer (EOC) diagnosed and treated in a Spanish population.

Materials and Methods: Retrospective cohort of patients with epithelial ovarian cancer who had neutrophil and lymphocyte values in complete blood count before the histopathological diagnosis and survival of at least three months, in an intermediate complexity hospital. Convenience sampling. Measured variables included age, menopausal stage, parity, International Federation of Gynecology and Obstetrics (FIGO) stage, treatment type, residual tumor, lymph node involvement, presence of ascites, cytology, histologic type, differentiation grade, and CA-125 values. Additionally, outcomes, overall survival, disease/progression-free survival were also measured. Bivariate inferential and Cox regression analyses were performed.

Results: Out of 78 candidates, 60 women with EOC were included. Of them, 24 (40%) had a low NLR (≤ 2,9) while 36 (60%) had a high NLR (> 2,9). An association was found between high NLR levels and suboptimal cytoreductive surgery. High NLR ratios were associated with lower overall survival (Hazard ratio (HR): 4.1; 95% CI: 1.4-11.8) and lower 5-year disease-free survival (HR: 2.6; 95% CI: 1.2-5.7).

Conclusions: A plasma neutrophil to lymphocyte ratio of more than 2.9 was associated with poor prognosis in patients with epithelial ovarian cancer in our setting. There is a need to establish the optimal cut-off point and conduct prospective studies with larger patient numbers in order to support this information.

Keywords: ovarian cancer; neutrophils; lymphocytes; prognosis; obstetrics; gynecology.

RESUMEN

Objetivos: evaluar si hay asociación entre los valores del cociente plasmático neutrófi-los/linfocitos (NLR) y el pronóstico en pacientes con cáncer epitelial de ovario (CEO) diagnosticadas y tratadas en una población española.

Materiales y métodos: cohorte retrospectiva de pacientes con cáncer epitelial de ovario que tuvieran

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un recuento de neutrófilos y linfocitos en hemograma previo al diagnóstico histopatológico en un hospital de nivel medio de complejidad y posterior sobrevida de, al menos, 3 meses. Muestreo por conveniencia. Se midieron: edad, estado menopáusico, paridad, estadio Federacion International de Ginecología y Obstetricia (FIGO), tipo de tratamiento, tumor residual, afectación ganglionar, presencia de ascitis, citología, tipo histológico, grado de diferenciación y cifras de CA-125; así mismo, desenlace, sobrevida global y sobrevida libre de enfermedad o progresión. Análisis inferencial bivariado y por regresión de Cox, para estimación de la razón de las tasas de incidencia. **Resultados:** de 78 candidatas, ingresaron 60 mujeres con CEO. De ellas, 24 (40%) presentaron un NLR bajo (≤ 2,9) y 36 (60 %) elevado (> 2,9). Se encontró asociación entre los niveles altos de NLR y cirugía cito-reductora subóptima. Los niveles altos de NLR se asociaron a menor sobrevida global (Hazard ratio (HR): 4,1; IC 95%: 1,4-11,8) y menor sobrevida libre de enfermedad a los 5 años (HR:2,6; IC 95 %: 1,2-5,7). **Conclusiones:** un cociente plasmático neutrófilos/linfocitos mayor de 2,9 se asoció a un mal pronóstico en pacientes con cáncer epitelial de ovario en nuestro medio. Se necesita determinar el punto de corte óptimo y realizar estudios prospectivos con mayor número de pacientes que avalen esta información.

Palabras clave: cáncer de ovario; neutrófilos; linfocitos; pronóstico; ginecología; obstetricia.

INTRODUCTION

Epithelial ovarian cancer (EOC) is the eighth most frequent cancer in women worldwide. It accounts for 4-5% of tumors affecting women, with an age-adjusted incidence rate of 7.1 x 100,000 people/year and a mortality rate of 4.1 x 100,0000 women/year in developed countries after breast, lung, gastrointestinal and cervical cancer, and it accounts for 4.7% of all female deaths due to cancer (1). In Spain, nearly 3,500 cases are diagnosed every year, with an adjusted incidence of 7.3 x 100,000 people/year and a mortality rate of 3.8 x 100,000 women/year. EOC is the primary cause of death due to gynecological cancer and kills approximately 2,000 of these women (2,3). EOC is a solid tumor of unknown etiology.

Despite advances in surgical treatment and the use of oncologic drugs, 5-year overall survival of patients with EOC is 48% and drops to 30% in advanced stages (III-IV) (4). High mortality is due to the fact that 75% of the patients are diagnosed at an advanced stage due to the absence of symptoms in the initial phases and non-specific abdominal discomfort in advanced stages of the disease, leading to the inability to develop effective screening that can lower mortality (5). None of the classic factors such as age, histologic type or FIGO (International Federation of Gynecology and Obstetrics) stage can provide an accurate estimate of response to treatment or patient prognosis. The only independent prognostic factor identified in advanced stages is complete cytoreduction (6). For this reason, biological markers, including, for example, inflammatory response markers, are needed to guide diagnosis and the selection of more individualized treatment options (7).

In terms of the inflammatory component, Balkwill and Mantovani described the relationship established by Virchow in 1863 between inflammation and cancer when he observed leukocyte infiltrates in neoplastic tissues (8). However, it was only recently that the important role of inflammation and immune cells in tumor development and progression of malignant neoplasms of different origin was established (9). As for cancer development, an association has been found with secondary inflammation following viral or bacterial infections, or the presence of environmental agents such as asbestos, or conditions leading to chronic inflammatory states, given their shared molecular signaling pathways (10). On the other hand, in tumors, neoplastic cells, normal cells and inflammatory cells constitute a tumor immune or inflammatory microenvironment (11) which, under certain stimuli, modulates the immune response and modifies its biologic conditions, favoring increased vascular permeability, angiogenesis, cell proliferation and mobilization, thus stimulating

tumor growth and distant spread (10). This is how some authors have reported an association between these inflammatory markers and poor prognosis or advanced stages of the disease (7,12-17).

One of these markers is the plasma neutrophil to lymphocyte ratio (NLR) which has been proposed as a simultaneous representative of the inflammatory process and the immune system, in such a way that a high NLR would reflect excess neutrophil activity or deficient lymphocyte activity, favoring higher protumor activity (18). As far as EOC is concerned, it has been shown that beneath risk factors such as the use of talcum powder or ovulation, is an underlying state of inflammation associated with high NLR values (19). On the other hand, higher risk states for disease in general and for cancer in particular, such as obesity and smoking, are associated with a high NLR. Moreover, when weight normalizes or there is smoking cessation, the risk as well as the levels of NLR and leukocytes drop (20,21). A relationship has also been found, with promising results to date, with prognosis of patients with different solid tumors, including gynecological tumors, EOC among them (20-22).

In EOC, a significant association has been found between a high NLR and the presence of poor prognostic factors such as ascites, elevated CA-125, advanced disease stage and residual tumor (23,24). Furthermore, there are data to suggest that cytoreduction may contribute to restore the balance between the immune response and the inflammatory state (25). However, other authors have reported low prognostic performance of NLR in EOC (26), particularly in terms of overall survival (27).

Therefore, the objective of this study is to determine if there is an association between NLR and prognosis in patients diagnosed and treated for epithelial ovarian cancer in a Spanish population.

MATERIALS AND METHODS

Design and population. Historical cohort which included patients with a histopathological diagnosis of invasive epithelial ovarian cancer treated with an intention to cure who had neutrophil and lymphocyte values in a complete blood count prior to the histopathological diagnosis of EOC, and who had at least three months of survival since the initiation of treatment in the Obstetrics and Gynecology Service of the Álvarez Buylla Hospital, Mieres, between April 1, 2012, and April 1, 2020. This hospital is a public, intermediate complexity institution located in the Autonomous Principality of Asturias (Spain), serving an area of 70,000 inhabitants. Excluded from the study were pregnant women, patients with other coexisting tumors, or patients diagnosed with an inflammatory or infectious process that required admission within the four weeks prior to the CBC, and women with an autoimmune disease or immunodeficiency. Consecutive sampling was used and study power was estimated, based on the observed overall survival in the results.

Procedure. The tumor registry of the hospital was searched in order to identify entries that included the terms cancer, epithelial and ovary. Electronic clinical records were then reviewed to extract clinical and follow-up data which were then entered in the SPSS 20 software as a database (JVR, JVR). Patients were staged in accordance with the 2009 FIGO criteria.

The surgical treatment consisted of primary surgery in those cases in which optimal cytoreduction was considered possible, or interval surgery in those where it was not. The decision was based on the findings of a diagnostic laparoscopy performed before treatment or imaging and biopsy or pleural effusion cytology (thoracoabdominal-pelvic CT scan). The surgery consisted of median suprainfraumbilical laparotomy with total hysterectomy, bilateral adnexal resection, omentectomy, pelvic and para-aortic lymphadenectomy when necessary, with multiple peritoneal biopsies. After the surgery, the residual tumor (RT) was defined as optimum if smaller or equal to 1 cm in size, and as suboptimal if larger in size. In accordance with the 2014 recommendations from the Spanish Society of Gynecology and Obstetrics (SEGO), chemotherapy

was given to patients with clear cell tumors in stages greater than IA-B GI. Chemotherapy consisted of 6 cycles of carboplatin (AUC 6) and paclitaxel (175 mg/m2) as an adjunct to primary cytoreduction, or 3 cycles before and 3 cycles after interval surgery. This rule was consistent during the study period. At the completion of treatment, patients were followed on an outpatient basis with clinical examination and CA-125 determinations at each follow-up visit conducted every 3-4 months during the first two years and every 6 months afterward. After year 5, the patients were followed every year. Imaging studies were indicated on an individual basis, driven by clinical suspicion or elevated CA-125 on two occasions. All patients had al least 7 months of follow-up if they were alive at the time of the study and 3 months if they had died.

CA-125, neutrophil and lymphocyte determinations were made in blood samples closest to the histological diagnosis of EOC made on surgical specimen or biopsy. CBC values were determined using the Automated Hematology Analyzer model XN-10 (Sysmex Corporation, Kobe, Japan). The NLR index was calculated as the ratio between absolute neutrophil and lymphocyte numbers.

Measured variables: Age, menopause, and parity were the sociodemographic variables. Clinical and pathological variables were treatment (primary or interval surgery), ascites (presence or absence), cytology study of ascitic fluid or pelvic lavage, histological type and grade, FIGO stage (with diagnostic laparoscopy, pleural effusion cytology or primary surgery), histologic lymph node status if lymphadenectomy was required, residual tumor following cytoreduction (smaller or larger than 1 cm) and CA-125 levels before treatment. Overall survival time was established from the moment of histological diagnosis until death or until the last follow-up in live patients. Disease-free survival time was measured from the moment of surgical treatment until recurrence when no residual tumor remained after surgery. Progression-free time was considered to exist when residual tumor remained after surgery with partial response or stable disease after the administration of chemotherapy until progression. This was defined on the basis of imaging studies (RECIST criteria [Response Evaluation Criteria in Solid Tumors] for solid tumors) and the CA-125 marker. Survival periods in patients who were disease-free or still alive, or who had died from other causes, were censored with the last follow-up date.

Statistical analysis. Descriptive statistics were used to summarize continuous variables by means of the relevant central trends and scatter. Distribution type (normal or non-normal) was estimated using the Kolmogorov-Smirnov test. Categorical variables were summarized using relative frequency. For the bivariate analysis, the Student t test was applied for normal distribution in order to detect differences between two groups, while the Mann-Whitney test was used for non-normal distribution. In a 2.9 value, the chi-square test was used to analyze differences between proportions in categorical variables (qualitative) and for dichotomous NLR. The optimal cutoff point was estimated by means of the ROC curve for 35-month survival (median follow-up) and was estimated at 2.9 with 77% sensitivity and 50% specificity, and 66% AUC ($p = 0.03$).

Disease/progression-free and overall survival curves as a function of dichotomous NLR were established in accordance with the Kaplan-Meier method and compared using the log-rank test. The association between NLR levels and overall survival, disease-free or recurrence-free survival was also assessed using the hazard ratios by means of the Cox proportional hazards model. This model was also used to estimate the univariate association between the NLR and clinical and pathological factors such as age, menopause, treatment, presence of ascites, ascitic fluid cytology, histologic type and grade, stage, lymph node stage, residual tumor and CA-125 level. The significance level was set at $p < 0.05$. All calculations were performed using the SPSS 20.0 software package.

Ethical considerations. The work was approved by the Research Ethics Committee of the Principality of Asturias and by the Research Committee of the Alvarez Buylla Hospital of Mieres (TFG 2020. 501).

RESULTS

Overall, 78 patients with a diagnosis of EOC were identified in the institutional tumor registry. Eighteen were excluded: 6 with a borderline tumor, 3 with other synchronous tumors (breast and endometrial cancer), 5 on palliative care at the start, 1 carcinosarcoma, 1 pseudomyxoma, 1 pregnant woman, and 1 with a concomitant acute inflammatory process (septic picture). In the end, 60 (82%) patients with EOC were included in the study (Figure 1).

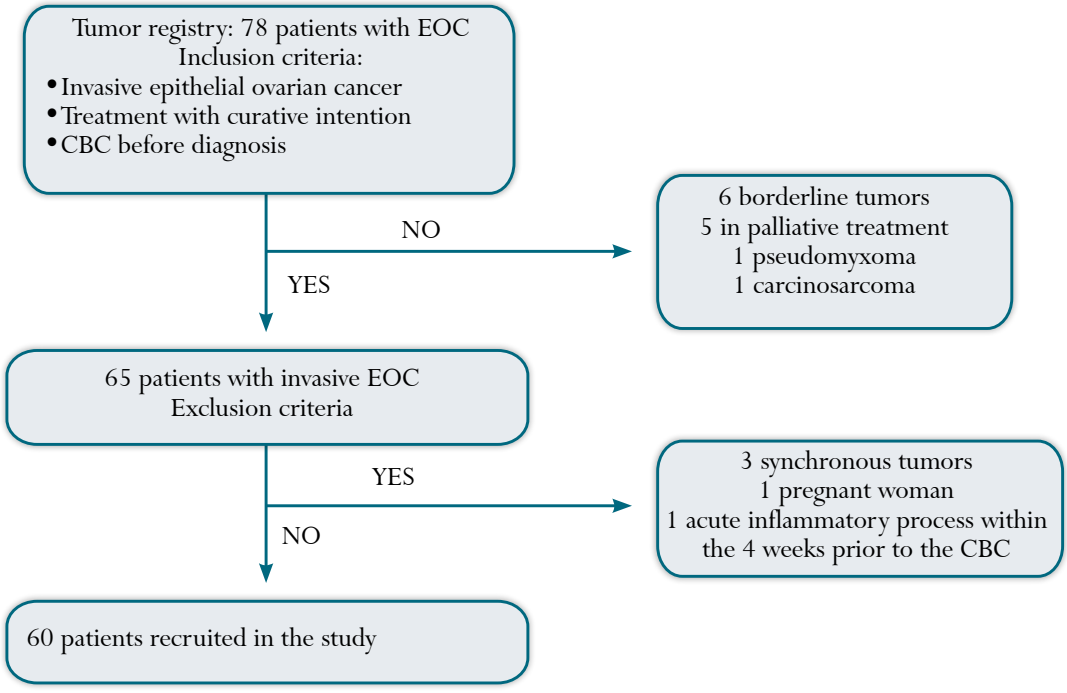

Figure 1. Flow diagram used for the selection of EOC patients.
Source: own elaboration.

In terms of patient and EOC clinical characteristics, the mean age was 62.9 (SD ± 11.8 years); the majority (83%) were menopausal women and with children (73%), in an advanced stage of the disease (n = 41; 68%) and with ascites (68%). Of the EOCs, 75% (n = 45) were high grade serous tumors (except for 1 low-grade tumor), 7% were mucinous, 3% endometrioid and 15% clear cell tumors. Primary cytoreduction was the treatment of choice in 33 patients (55%), while 27 patients (45%) received chemotherapy followed later by interval surgery. In 5 of them (18%) interval surgery was never performed due to disease progression.

The time between CBC sampling and histopathological diagnosis ranged from 1 to 30 days, with a mean of 11 days (SD ± 7). NLR values ranged between 1 and 11.75, with a median of 3.3 (IQR [interquartile range]: 2.3-4.9). The group with a low NLR (≤ 2.9) consisted of 24 patients (40%) while the group with the high NLR (> 2.9) consisted of 36 patients (60%). Factors associated with a high NLR level included the type of treatment used in the group of patients and the presence of residual tumor following cytoreductive surgery for advanced stages (Table 1).

Table 1.
Baseline characteristics of patients with epithelial ovarian cancer and their relationship with NLR values. Hospital Álvarez Buylla, Mieres (España), 2012- 2020.

	NLR		
	< 2,9	> 2,9	p*
Number of patients	24 (40)	36 (60)	
Age (mean ± SD)	62 ± 10.7	63 ± 12.7	0.8‡
Menopause			1
No	4 (16)	6 (16)	
Yes	20 (83)	30 (83)	
Parity			0.8
0	6 (25)	10 (27)	
≥ 1	18 (75)	26 (72)	
Stages			0.1
Early (I-II)	10 (41)	9 (25)	
Advanced (III-IV)	14 (59)	27 (75)	
Treatment			0.04
Primary surgery	17 (70)	16 (44)	
Neoadjuvant therapy	7 (30)	20 (56)	
Advanced stages			0.1
Primary surgery	7 (50)	7 (26)	
Neoadjuvant therapy	7 (50)	20 (74)	
Ascites			0.08
No	10 (41)	7 (20)	
Yes	14 (58)	27 (79)	
Unknown		2	
Histologic type			0.5
Serous	19 (79)	26 (72)	
Non serouos	5 (21)	10 (28)	
Grade			0.7
I-II	4 (18)	6 (21)	
III	18 (81)	22 (78)	
No grade	2	8	
Cytology			0.9
Negative	11 (45)	15 (47)	
Positive	13 (54)	17 (53)	
Undetermined		4	
Lymph nodes			0.6
Negative	16 (84)	15 (78)	
Positive	3 (16)	4 (22)	
No lymphadenectomy	5	17	
Advanced stages			0.01
Optimum surgery (RT ≤ 1 cm)	14 (100)	18 (66)	
Suboptimal surgery (RT > 1 cm)	0	9 (33)	
CA-125			0.2
< 35 mIU/ml	4 (18)	3 (8)	
> 35 mIU/ml	18 (82)	32 (92)	
Unknown	2	1	

* Chi-square test.
‡ Student t test.
Source: own elaboration.

Median follow-up was 35 months. Disease-free survival was assessed in 44 patients (recurrence occurred in 20), and progression-free survival was assessed in 16 (14 had progression). In total, 34 patients experienced recurrence/progression (with a 5-year likelihood of disease/progression-free survival of 36%, and 22 patients died as a result of the disease, with an overall 5-year survival likelihood of 57%.

Five-year disease-free survival was 17% in patients with a high NLR, versus 51% in patients with low NLR (HR [Hazard ratio]: 2.6; 95% CI: 1,2-5,7). In patients with a high NLR, overall 5-year survival was 37% vs. 83% in patients with NLR < 2.9 (HR: 4.1; 95% CI: 1.4-11.8) (Table 2, Figure 2). With these observed overall survival data difference and the number of patients in the sample, statistical power was 85%. Patients with ascites, serous tumors, advanced stage, positive lymph nodes, RT > 1 cm or who needed neoadjuvant therapy, had a higher risk of 5-year mortality (Table 2).

Table 2.
Clinical and treatment variables and 5-year overall survival in patients with epithelial ovarian cancer, Hospital Álvarez Buylla, Mieres (Spain), 2012-2020.

		Mortality
	HR*	**IC 95 %**
Advanced stages Primary surgery** Neoadjuvant therapy	3.7	1.05-12.9
Ascites No** Yes	9.3	1.2-70.1
Stages Early (I-II)** Advanced (III-IV)	41	1.1-158
Lymph nodes Negative** Positive	5.6	1.3-23.2
Advanced stages (RT) Optimal surgery (RT ≤ 1 cm)** Suboptimal surgery (RT > 1 cm)	7.2	2.4-20.0
NLR < 2,9 ** > 2,9	4.1	1.4-11.8

*HR estimated for univariate analysis using Cox regression.
** Baseline risk category.
HR: Hazard ratio; 95% CI: 95% confidence. HR estimated from non-adjusted Cox models.
Source: own elaboration.

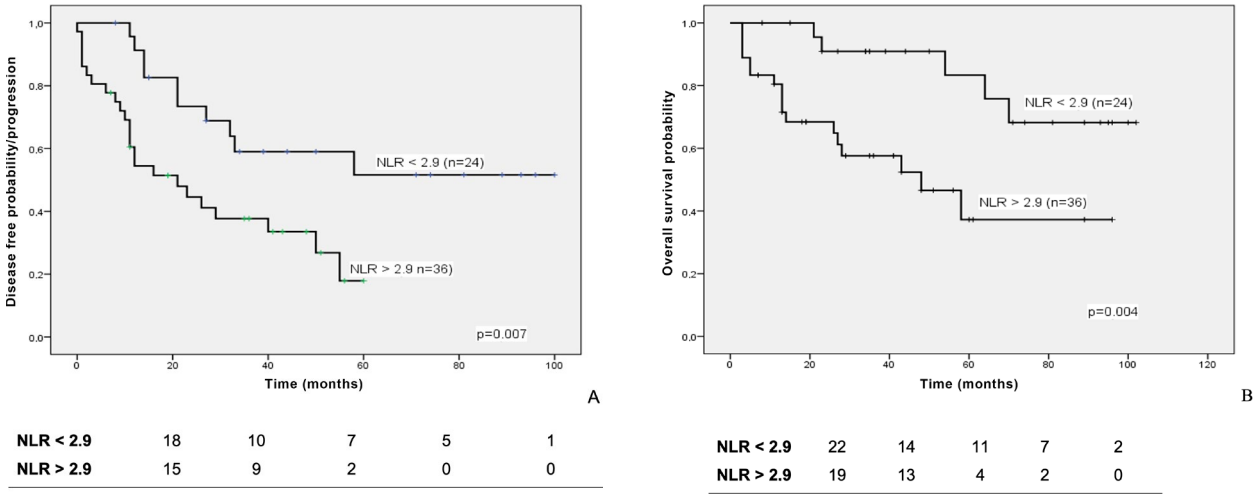

Figure 2. Time to death analysis. Kaplan Meier curves of the cumulative estimate of dis-ease-free survival (A) and overall survival (B) of patients with EOC as a function NLR.
Source: own elaboration.

DISCUSSION

This study found a potential association between a high NLR and lower 5-year overall survival and disease-free survival in patients receiving treatment for EOC. Moreover, a high NLR was associated with the type of treatment and the presence of residual tumor > 1 cm after cytoreductive surgery in advanced stages.

Regarding overall survival, our observations are consistent with the systematic review reported by Zhang in 2023, which included 21 studies (28). On the other hand, they are in contrast with other studies such as that by Badora-Rybicka et al. (29) who report that the NLR is not a good predictor of survival, while other authors report poor prognostic performance for NLR in EOC (26), especially in terms of overall survival. (27) These contradicting results could be attributed to factors such as genes, resistance to chemotherapy or biology (24). Regarding higher disease-free survival, our observations are consistent with the systematic review by Zhang et al. that shows shorter disease-free time and lower survival in patients with an elevated NLR. (28)

Regarding the association between high NLR and suboptimal cytoreduction, our data are similar to those reported by Williams et al. in a sample of 519 patients with EOC in the United States (19) and by Feng et al. in China in 875 women with EOC, applying a cutoff level of 3.24 (30). In terms of the non-association between ascites and CA-125 with a high NLR, our results differ from the findings of the two authors mentioned above. Additionally, we did not observe differences in terms of stage, which is not consistent with the report by Marchetti et al. that 94% of patients with high NLR were stage III-IV, vs. 72% in earlier stages (23).

These differences among authors could be due to the lack of an optimal cutoff point to classify patients as having a high or low NLR. In general, it ranges between 2.3 and 4 in the different papers, when applying mean, median and, in most cases, the ROC (receiver operating characteristic) curve (28). In our work, the optimal cutoff point for overall survival was 2.9, falling within the range of the other studies.

As for strengths and weaknesses, NLR is a standardized quantifiable plasma marker within the reach of any laboratory. Our study is strong in that all plasma determinations were done in the same laboratory and patients were managed in a single institution under a unified approach in terms of diagnosis, treatment and follow-up. However, being a retrospective study, it has limitations. A multivariate analysis was no possible due to insufficient sample size, and failure to adjust type I error by multiple comparisons. On the other hand, there are factors that can lead to a "false" increase in NLR, including

age; exogenous use of steroids; active hematological disorders such as leukemia; cytotoxic chemotherapy, or granulocyte colony stimulating factor (G-CSF), which were not assessed in this study.

Furthermore, it would be interesting to examine the correlation between plasma NLR and intra-tumor neutrophils and lymphocytes, as well as postoperative changes in NLR values.

CONCLUSIONS

An NLR value higher than 2.9 was associated with poor prognosis in patients with epithelial ovarian cancer in our setting.

An optimal cut-off point needs to be reported and prospective studies with a larger number of patients are needed in order to support this information.

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AUTHORS' CONTRIBUTIONS

Julio Vázquez Rojo: Study planning, data analysis and interpretation and main responsibility for the discussion, approval of the final version of the paper. Julio Vázquez Reguera: Data collection, information and review of the literature, approval of the final version of the paper.

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