

Aim of the study: Our aim was to analyse the feasibility of white blood cell and platelet counts along with their ratios as a prognostic factor in patients who underwent surgery for ovarian mass.

Material and methods: We retrospectively studied the patients admitted in the Department of Gynaecology due to adnexal mass. The potential association of the neutrophil-to-lymphocyte-ratio (NLR), neutrophil-to-monocyte (NMR), platelet-to-lymphocyte (PLR), lymphocyte-to-monocyte (LMR), monocyte-to-platelet, and malignancy was evaluated.

Results: Patients with malignant tumours were found with significantly higher ratios of NLR ($p < 0.001$) and PLR ($p < 0.001$) and lower LMR ratio ($p < 0.001$) compared to those with benign tumours. Furthermore, higher lymphocyte count ($p = 0.04$) and platelet count ($p = 0.004$) were found in cancer patients when compared with borderline tumours. No significant variations were detected regarding white blood cell count ($p = 0.238$), NMR ratio ($p = 0.28$), platelet-to-neutrophil ratio ($p = 0.12$), and platelet-to-monocyte ratio ($p = 0.34$).

Conclusions: Inflammation biomarker ratios can easily and inexpensive assist in distinguishing malignant ovarian tumours from benign ones.

Key words: pelvic tumours, inflammation biomarkers, differential diagnosis.

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The role of inflammation biomarkers in differential diagnosis of pelvic tumours of ovarian origin: a single-centre observational study

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Introduction

Ovarian cancer (OC) constitutes the 5th most common female cancer worldwide. According to the statistics of 2012, 65,900 and 86,000 women in economically developed and developing countries, respectively, died due to the disease [1]. During the last decades, OC has remained the most lethal malignancy among women worldwide, with a median overall survival which barely reaches 30% [2]. Histological grade and staging of the disease, number of resected lymph nodes, increased values of tumour markers such as human epididymis protein 4 (HE4) and cancer antigen 125 (CA125), as well as the risk of malignancy index and the risk of malignancy algorithm have been demonstrated to have high predictive and prognostic significance in patients with OC [3, 4]. However their application in clinical practice is limited due to the lack of standardization and high cost [5]. Furthermore, recently, an increasing interest in the association between inflammation and cancer has been widely expressed [5]. Inflammation has been reported as a significant risk factor that predisposes to alternation of tissues from premalignant to malignant. In that setting, the inflammation process can cause cell turnover, and the created microenvironment can often lead to an increase in DNA damage or mutation [6].

Neutrophils, lymphocytes, monocytes, platelets, and their ratios, specifically the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have been proposed as useful biomarkers in the diagnosis and management of various cancers, including endometrial, cervical, pancreatic, gastric, and breast cancer [7–10]. The application of NLR and PLR ratios as a screening test in patients with adnexal tumours has been investigated by several studies [11, 12]. Nonetheless, the clinical utility and the association of these biomarkers with prognosis in patients with pelvic tumours has yet to be elucidated.

In this study we aimed to evaluate the utility of inflammatory ratios as a prognostic factor in women undergoing surgery for an ovarian mass.

Material and methods

Study population

A retrospective analysis of patients who were admitted in the Department of Gynaecology of the Metaxa Memorial Cancer Hospital of Piraeus from May 2016 to May 2018 due to adnexal mass was performed. The Institutional Review Board or Ethics Committee approved our research protocol before

the initiation of the study, and all human participants and their parents gave written/verbal informed consent. All women were preoperatively evaluated with ultrasonography (US) and/or computer tomography and/or magnetic resonance. All of them underwent surgery with the intention to treat or to stage their disease. Levels of preoperative neutrophils, lymphocytes, monocytes, and platelets were measured and NLR, PLR, lymphocyte-to-monocyte (LMR), and platelet-to-monocyte ratio (PMR) were then calculated. The pathology department of our hospital conducted the histopathological analysis and characterized the resected specimens as malignant, borderline, or benign. Finally, the examined ratios were correlated to the histological type of the resected masses. A sub-analysis according to stage and grade of malignant tumours was also performed.

NLR, PLR, LMR, and PMR calculation

The absolute neutrophil count was divided by the absolute lymphocyte count to determine the NLR; Respectively, PLR was determined by dividing the absolute platelet count by the absolute lymphocyte count, LMR by dividing the absolute lymphocyte count by the absolute monocyte count, and PMR by dividing the absolute monocyte count by the absolute platelet count.

Statistical analysis

The Shapiro-Wilk test was used to estimate the normality of data distribution. Student's t-test, Welch test, or Mann-Whitney U test were performed as appropriate to perform comparisons between 2 groups, while the comparisons among 3 groups were performed using the analysis of variance (ANOVA) with the Bonferroni correction or the Kruskal-Wallis test with the Bonferroni correction, as appropriate. Correlations between 2 continuous variables were assessed using Pearson's correlation coefficient or Spearman's rank correlation coefficient, as appropriate. To identify the optimal cut-off points for parameters that provided significant results, we used a combination of the receiver operating characteristic curve and Youden's J statistic. Sensitivities and specificities were calculated based on these optimal cut-off points. All the tests were 2-tailed. Results were considered statistically significant if the *p*-value was less than 0.05. The statistical analysis was performed with the 25th edition of the Statistical Package for the Social Sciences (IBM, Armonk, NY, USA).

Results

One hundred and seventy-nine women presenting with ovarian tumours were included in our study. One hundred and twenty-four had benign tumour (69.3%), 9 had borderline tumour (5%), and 46 had malignant tumour (25.7%). The mean age was 53.5 years (SD: 15), and the median age was 53 years (min-max: 20–86). Ninety-seven women were premenopausal, and 82 women were postmenopausal. Among patients with malignant disease, 9 were diagnosed with stage I disease, 4 with stage II, 32 with stage III, and 3 with stage IV.

Comparison among tumour groups

Borderline and malignant tumours were more frequent in postmenopausal women than in premenopausal women [premenopausal: benign: 76/97 (78.4%), borderline: 3/97 (3.1%), malignant: 18/97 (18.6%), postmenopausal: benign: 48/82 (58.5%), borderline: 6/82 (7.3%), malignant: 28/82 (34.1%) (*p* = 0.015)]. With regards to leukocyte and platelet indices, malignant tumours had higher neutrophil count (median: 5432, min-max: 2042–9219 vs. median: 4326.5, min-max: 2169–15306, *p* = 0.013), monocyte count (median: 470.5, min-max: 269–828 vs. median: 402, min-max: 169 vs. 1574, *p* = 0.042), platelet count (median: 307,000, min-max: 149,000–884,000 vs. median: 265,000, min-max: 147,000–4,660,000, *p* < 0.001), NLR (median: 2.8, min-max: 1.2–17.4 vs. median: 2.1, min-max: 0.8–8.8, *p* < 0.001), and PLR (median: 184.2, min-max: 76.1–502.8 vs. median: 128.4, min-max: 35.6–332.1, *p* < 0.001), and lower lymphocyte count (median: 1786.5, min-max: 458–3887 vs. median: 2176, min-max: 972–5219, *p* = 0.004) and LMR (median: 3.8, min-max: 1.3–9.7 vs. median: 5, min-max: 1.7–11.4, *p* < 0.001) when compared with benign tumours. Moreover, malignant tumours had higher lymphocyte count (median: 1786.5, min-max: 458–3887 vs. median: 1652, min-max: 481–2343, *p* = 0.04) and platelet count (median: 307000, min-max: 149,000–884,000 vs. median: 236,000, min-max: 162,000–300,000, *p* = 0.004) when compared with borderline tumours. On the other hand, no significant variations were detected regarding white blood cell count (*p* = 0.238), NLR (*p* = 0.28), PLR (*p* = 0.12), and PMR (*p* = 0.34).

Differentiating malignant from benign/borderline tumours

Leukocyte and platelet indices provided mediocre results. In particular, the AUC for neutrophil count was 0.638 (SE: 0.05, 95% CI: 0.54–0.736, *p* = 0.005), the AUC for lymphocyte count was 0.644 (SE: 0.046, 95% CI: 0.555–0.734, *p* = 0.004), the AUC for monocyte count was 0.627 (SE: 0.047, 95% CI: 0.535–0.72, *p* = 0.01), the AUC for platelet count was 0.703 (SE: 0.048, 95% CI: 0.609–0.798, *p* < 0.001), the AUC for NLR was 0.69 (SE: 0.046, 95% CI: 0.6–0.779, *p* < 0.001), the AUC for LMR was 0.712 (SE: 0.045, 95% CI: 0.623–0.801, *p* < 0.001), and the AUC for PLR was 0.759 (SE: 0.044, 95% CI: 0.674–0.845, *p* < 0.001). The optimal cut-off points for identifying malignancy were the following: neutrophil count: ≥ 6184.5 (sensitivity: 41.3%, specificity: 85%), lymphocyte count: ≤ 2303 (sensitivity: 89.1%, specificity: 40.6%), monocyte count: ≥ 452.5 (sensitivity: 65.2%, specificity: 63.9%), platelet count: $\geq 284,500$ (sensitivity: 69.6%, specificity: 67.7%), NLR: ≥ 2.4 (sensitivity: 67.4%, specificity: 65.4%), LMR: ≤ 4.55 (sensitivity: 71.7%, specificity: 65.4%), and PLR: ≥ 181.1 (sensitivity: 60.9%, specificity: 83.5%).

Differentiating malignant/borderline from benign tumours

Leukocyte and platelet indices provided mediocre results. In particular, the AUC for neutrophil count was 0.629 (SE: 0.047, 95% CI: 0.537–0.721, *p* = 0.006), the AUC for lymphocyte count was 0.675 (SE: 0.042, 95% CI: 0.592–

Table 1. Values of the examined biomarkers and statistical significance of comparison among the groups

	Benign (n = 124)	Borderline (n = 9)	Malignant (n = 46)	p-value malignant vs. benign	p-value malignant vs. borderline
Neutrophil count					
Mean	4751	5582	4950	0.013	0.238
Median	4436	5139	5432		
SD	1978.29	1619.73	1957.55		
Range	13137	5134	7177		
Lymphocyte count					
Mean	2190.94	1556.11	1802.95	0.004	0.04
Median	2176	1652	1786.5		
SD	687.66	613.90	612.85		
Range	4247	1862	3429		
Monocyte count					
Mean	443.47	400.55	496.02	0.042	NS
Median	402	362	470.5		
SD	179.96	154.29	147.66		
Range	1405	489	559		
Platelet count					
Mean	271,911.29	235,222.22	344,565.21	< 0.001	0.004
Median	265,000	236,000	307,000		
SD	70,079.51	42,313.64	131,180.22		
Range	319,000	138,000	735,000		
NLR					
Mean	2.34	4.00	3.62	< 0.001	0.28
Median	2.14	3.18	2.80		
SD	1.18	2.69	2.64		
Range	8.01	7.91	16.23		
PLR					
Mean	134.59	180.68	210.61	< 0.001	0.12
Median	128.36	152.56	184.22		
SD	50.47	88.04	98.64		
Range	296.48	251.99	426.70		
LMR					
Mean	5.32	4.17	3.94	< 0.001	NS
Median	5.0	3.35	3.8		
SD	1.8	1.91	1.78		
Range	9.66	5.27	8.41		

SD – standard deviation

0.758, $p < 0.001$), the AUC for monocyte count was 0.593 (SE: 0.046, 95% CI: 0.502 vs. 0.684, $p = 0.048$), the AUC for platelet count was 0.639 (SE: 0.048, 95% CI: 0.545 vs. 0.732, $p = 0.003$), the AUC for NLR was 0.708 (SE: 0.043, 95% CI: 0.624–0.792, $p < 0.001$), the AUC for LMR was 0.716 (SE: 0.043, 95% CI: 0.632–0.801, $p < 0.001$), and the AUC for PLR

was 0.753 (SE: 0.041, 95% CI: 0.672–0.834, $p < 0.001$). The optimal cut-off points for identifying malignant/borderline tumours were the following: neutrophil count: ≥ 5136.5 (sensitivity: 58.2%, specificity: 67.7%), lymphocyte count: ≤ 2303 (sensitivity: 89.1%, specificity: 42.7%), monocyte count: ≥ 452.5 (sensitivity: 60%, specificity: 63.7%), plate-

let count: $\geq 284,500$ (sensitivity: 60%, specificity: 66.1%), NLR: ≥ 2.52 (sensitivity: 63.6%, specificity: 71.8%), LMR: ≤ 3.94 (sensitivity: 56.4%, specificity: 79.8%), and PLR: ≥ 142.7 (sensitivity: 78.2%, specificity: 64.5%) (Table 1).

Discussion

Systemic inflammatory response has been demonstrated to be associated with cancer progression and survival, and inflammation markers have been explored extensively as prognostic factors [10], with NLR specifically being suggested by many studies as significant [13]. Blood cell counts and their ratios, such as NLR, PLR, and LMR, are considered markers indicating systemic inflammation [14]. However, the exact role of those parameters in predicting the oncological outcome has not yet been elucidated. Our study sought to report a longitudinal comparison of 6 systemic inflammation-based prognostic ratios, and to evaluate their role in differentiating malignant from benign and borderline ovarian tumours. Our study suggests a strong association between the majority of the investigated biomarkers (NLR, PLR, and LMR) and detection of malignancy in patients with adnexal masses. No difference was found for NLR, PLR, and PMR ratios among patients with malignant and borderline disease.

Neutrophils are the white blood cells that control the inflammatory response of normal cells against cancer mutations. The cytokines that they secrete, such as interleukins and vascular endothelial growth factor, are responsible for activating various molecular pathways that interact with normal tissue cells and other inflammatory cells, such as platelets and lymphocytes, and prolong the inflammatory process [15]. Activated neutrophils block the cytotoxic activity of T-cell lymphocytes, resulting in an immunosuppressive tumour environment [16]. In this micro-environment, a sequence of molecular interactions is responsible for tumour spread, angiogenesis, and metastasis to distant sites [17].

Lymphocytes have been proposed to play a well-established role in cytotoxic cell death and cytokine cascade, preventing proliferation and metastatic activity of malignant cells. Additionally, lymphocytes known as tumour infiltrating lymphocytes have been detected in the tumour site and play an important role in killing tumour cells and preventing tumour genesis and metastasis [2, 18]. They have been described in many cancers, including OC, and have been associated with good prognosis [15].

Monocytes, on the other hand, are transformed into macrophages when attracted by factors that tumour cells produce and have cytotoxic activity, destroying cancer cells. However, tumour-associated macrophages also have other different functions that trigger chronic inflammation and secrete cytokines that enhance oncogenesis and metastasis by creating an immunosuppressive environment around the tumour [1]. Therefore, when the monocyte count of the peripheral blood is higher than normal in a cancer patient, it is considered an adverse prognostic factor [1].

The role of platelets in tumour proliferation has been widely studied. Platelets are activated by the chronic in-

flammatory response and secrete TGF- β , which attracts neutrophils to the tumour site, which, as mentioned above, help tumour growth [1, 15]. Activated platelets trigger other mechanisms, such as thrombosis and angiogenesis and, eventually, metastasis [15]. An increased platelet number in the peripheral blood is described in many cancers, including ovarian cancer: more than a fifth of patients with epithelial ovarian cancer (EOC) have thrombocytosis [18]. Thrombocytosis at the time of diagnosis is related to poor survival and resistance to chemotherapy [18].

NLR constitutes an inflammation marker [16, 18], possibly able to differentiate malignant from benign ovarian tumours [19]. High NLR score refers to a high neutrophil count and a low lymphocyte count in the patient's serum. Yildirim *et al.* found a sensitivity and specificity of 65% and 72%, respectively, for the early diagnosis of EOC [11]. This ratio was found to be higher in advanced-stage OC and high histological grade [19, 20]. An elevated NLR score has been related to an unfavourable response to chemotherapy [20]. According to Miao *et al.*, elevated NLR can predict chemoresistance with a sensitivity of 75% and a specificity of 80% [20]. Thus, NLR and prognosis and overall survival of EOC are closely related. Elevated NLR values have been linked to poor prognosis, overall survival, and progression-free survival [2, 16]. Ashrafganjoei *et al.* demonstrated that NLR could predict surgical outcome in EOC patients, with a reported sensitivity of 74% and of specificity 58%. These findings are in harmony with those of our analysis, because NLR and PLR also showed diagnostic sensitivity in OC (AUC = 0.69, AUC = 0.759). Interestingly, these results are encouraging compared to those of other studies analysing the same ratios in non-gynaecological malignancies. Machairas *et al.* concluded that white blood cell and platelet counts cannot assist in diagnosing early thyroid cancer [10], while other studies examining a potential link between the inflammation biomarkers NLR and PLR and neoplasms of the gastrointestinal track, although demonstrating a significant diagnostic value, lack a detailed discussion of specificity and sensitivity [9, 14].

PLR can also predict malignancy of an adnexal tumour when assessed preoperatively (sensitivity 74%, specificity 67%) whereas elevated PLR levels can negatively affect the survival of patients with EOC [17]. Increased levels of PLR represent thrombocytosis in the peripheral blood and consequently can indicate resistance to chemotherapy (sensitivity 60% and specificity 85%) [21].

LMR can also serve as a prognostic factor for ovarian malignancies [1]. Low LMR scores are related to a high monocyte count, and therefore an unfavourable prognosis and survival [1]. This association has been described in many cancers, such as Hodgkin's lymphoma and ovarian cancer. Unfortunately, there are not many studies in the literature examining the clinical utility of LMR. NLR and PLR have been demonstrated as useful predictors of malignancy. Our analysis highlights that additional ratios such as LMR can possibly be confirmed as prognostic biomarkers in ovarian cancer. However, the application of LMR as a screening tool in the general population has not been validated yet. Additionally, there are some further limitations before interpreting our outcomes that need to be addressed. First of all,

our study was performed during a limited period between 2016 and 2018. All gynaecological oncology operations were performed by our team led by 3 different consultants based on MDT decisions and international guidelines. For this reason, and because of the small period of the study (3 years), no significant change could be identified between changes over time or any therapy-dependent changes. Another weakness of the article is that our results cannot be clearly clinically useful yet.

Conclusions

Inflammation biomarkers can serve as significant indicators of malignancy in patients with ovarian tumours. The examined ratios depict the status of the immune system of the patient and are therefore potentially able to define the prognosis of ovarian malignancy. They comprise an easily calculated and inexpensive test that can be easily utilized in everyday clinical practice. Further research is warranted in this field to determine the predictive utility of the inflammatory biomarkers so as to routinely introduce them into clinical practice.

The authors declare no conflict of interest.

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