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Original Research Article

The diagnostic value of systemic inflammatory response markers as predictors of epithelial ovarian cancer

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ABSTRACT

Background: Early detection of ovarian neoplasms confers a better outcome and prognosis for patients. Although newer diagnostic modalities have been recently developed, the availability and accessibility of complete blood count parameters make it a convenient and cost-effective marker for malignancy. Objectives were to evaluate the diagnostic accuracy of pretreatment neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) in patients with late-stage epithelial ovarian malignancy at the University of Port Harcourt Teaching Hospital.
Methods: A prospective analysis of fifty-seven women with histologic diagnosis of epithelial ovarian cancer who were managed at the University of Port Harcourt Teaching Hospital between January 1, 2018, and December 31, 2022, was conducted. A data collection form was used to obtain socio-demographic and clinico-pathological characteristics from the patients after informed consent was obtained. Pretreatment levels of NLR and PLR were determined from complete blood count. The Receiver Operating Characteristic (ROC) curve analysis was used to assess the predictive accuracy of the haematological parameters for late-stage epithelial ovarian cancer.
Results: Higher values of NLR and PLR were significantly associated with the stage of ovarian cancer (p=0.001). The optimal cut-off points based on ROC curve analyses for NLR and PLR were found to be 2.6 (AUC=0.61, p>0.05), and 155.8 (AUC=0.62, p>0.05) respectively. However, none of the haematological parameters could be used as predictive markers for advanced-stage ovarian cancer in this study.
Conclusions: Pretreatment NLR and PLR cannot be used as a stand-alone predictor of advanced ovarian cancer, and should be correlated with other clinical, laboratory and radiologic parameters.

Keywords: Ovarian malignancy, Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio, Predictive value, Systemic inflammatory response markers

INTRODUCTION

Ovarian cancer is the world's second leading cause of gynaecologic cancer deaths, trailing only cervical cancer.[1] It is still the most lethal of all gynaecological cancers, with nearly two-thirds of patients diagnosed in an advanced stage. The 5-year overall survival rate for ovarian cancer is 48%. The prognosis differs according to the stage, histologic type, and chemotherapy sensitivity.[2] With a lifetime risk of 1 in 70, it is the leading cause of gynaecologic cancer deaths in most developed countries.[3] According to GLOBOCAN 2020; 313,959 new cases of ovarian cancer were diagnosed worldwide, with 207,252 deaths. It is the eighth most common cancer in females in terms of incidence (6.6%) and mortality (4.2%).[1]

Several studies in Nigeria have reported a general increase in the incidence of ovarian cancer. It accounts for 7-26% of all gynaecological malignancies, according to research from various Nigerian centres.[4-7] Ovarian cancer is a broad category of cancer. The most common type, accounting for

90% of all cases, is epithelial ovarian cancer (EOC).[8] EOC is most common in women aged 55 to 64 years, and deaths occur most frequently in women aged 75 to 84 years.[9] There is currently no available screening test for ovarian tumours.

In spite the fact that histological grading 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 shown to have high predictive and prognostic significance in patients with ovarian cancer, their application in clinical practice is limited due to a lack of standardization and high cost.[10-12] Proliferation of cancer cells, metastasis, and angiogenesis all stimulate the systemic inflammatory response.[13] Inflammation and immune response play important roles in cancer initiation and progression, and there is growing interest in the prognostic value of these responses.[14]

Several studies have shown the importance of the inflammatory response in the development and progression of cancer. Inflammatory cells play an important role in tumorigenesis. The relationship between complete blood count (CBC) parameters and cancer has been studied for many years. This inexpensive, less invasive, reproducible, and easily accessible test is routinely included in all admission and preoperative workups, making it a useful marker, specifically platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR).[15]

The pathophysiology of systemic inflammation supports the theory underlying the use of NLR. Inflammation raises the risk and progression of cancer and is known to play a role in tumorigenesis, which includes tumour initiation, promotion, malignant conversion, invasion, and metastasis.[15] Previous research on PLR has shown that increased production of thrombopoietic cytokines, particularly interleukin 6, leads to paraneoplastic thrombocytosis, which eventually leads to tumour growth and progression.[16] The degree of immune response inherent in solid tumours, represents the body's overall retortion to the tumour such that progression is associated with systemic inflammation.[17,18]

Chronic inflammation, on the other hand, is one of the factors that contribute to oncogenesis.[19] It has also been demonstrated that inflammatory markers increase significantly in various cancers. Recent studies on cancers in various organ systems, including prognosis, have focused on CBC parameters in inflammation.[20-23] The recent hypothesis that a microenvironment and subsequent remodeling and transformation of epithelial cells by proinflammatory cytokines initiate the development of epithelial ovarian cancers is of particular interest.[24] Because chronic inflammation is implicated in the pathogenesis of ovarian cancer, systemic inflammatory response markers such as neutrophil-lymphocyte ratio and platelet-lymphocyte ratio have been studied and advocated for due to their ease of use, availability, accessibility, and cost-effectiveness.

Several studies have found a relationship between advanced stage disease, decreased overall survival, and even adverse surgical and platinum-based therapy resistance with increasing NLR when used as a prognostic factor for disease stage, progression-free survival (PFS), and overall survival (OS).[25-27] PLR, like NLR, has been used as a prognostic factor for malignant epithelial tumours, and increased PLR levels are associated with advanced-stage disease, poor chemotherapy response, and poor surgical outcome.[26,28]

However, there is no conclusive evidence supporting the use of NLR and PLR as predictive markers in ovarian cancer. There are few and conflicting results from these studies, and it is still unclear how NLR and PLR affect prognosis in ovarian cancer. To provide evidence for clinical practice, the study set out to investigate the diagnostic accuracy of NLR and PLR in predicting the stage of ovarian cancer.

METHODS

Study area

This study was conducted at the gynaecologic oncology unit of the University of Port Harcourt Teaching Hospital (UPTH). The University of Port Harcourt Teaching Hospital is a 988-bed hospital in Alakahia, in Obio-Akpor Local Government Area of Rivers state. It is a tertiary hospital that serves as a referral centre for all levels of healthcare in Rivers state and other neighbouring states including Bayelsa, Imo and Abia. The gynaecologic oncology clinic runs every Friday, and each clinic session is led by a team of consultants. Patients are evaluated in the clinic before they are admitted into the gynaecogical ward for surgery. The haematology clinic runs twice a week and has two haematology auto analyzers for complete blood count analysis.

Methodology

This was a cross-sectional study of 57 women with histologically confirmed epithelial ovarian tumour managed at the University of Port Harcourt Teaching Hospital between January 1, 2018, and December 31, 2022. The purpose of the study was duly explained to the women and an informed consent obtained. A structured interviewer-administered questionnaire designed for this purpose was used to obtain socio-demographic, clinical, and haematological parameters. Each participant was assigned a unique identity to ensure anonymity and ease of identification. The data collection tools were checked daily for accuracy and completeness. The inclusion criteria were patients who have not received any form of treatment; age ≥18 years; and those with complete clinical data. The exclusion criteria were patients with other disease that

influenced significant amount of neutrophil, platelet, lymphocyte, or leukocyte, such as cardiovascular disease, renal disease, autoimmune disease, diabetes mellitus, and blood disease, concomitant with other malignant tumours, patients with co-infectious diseases such as viral infection at the time of admission.

Pre-treatment assessment and analysis of inflammatory markers

At the time of admission, all patients underwent physical and gynaecological pelvic examinations and ultrasonography. Lymph node involvement and distant metastasis were assessed using abdomino-pelvic computed tomography (CT) scan. The initial complete blood count was done at the time of admission. Absolute white blood cell (WBC) counts (AWC), absolute lymphocyte counts (ALC), absolute neutrophil counts (ANC), absolute monocyte counts (AMC), and absolute platelet counts (APC) were among the haematological parameters measured. NLR was calculated by dividing the absolute neutrophil count (ANC) by the absolute lymphocyte count (ALC). PLR was defined as the absolute platelet count (APC) divided by the absolute lymphocyte count (ALC). Thereafter, all patients had optimal cytoreduction, and specimens were sent for histopathological analysis to determine the stage and histological type of tumour. Optimal cytoreduction was considered as <1 cm of remaining tumour. The disease stage was evaluated according to International Federation of Gynaecology and Obstetrics (FIGO) 2009 criteria.

Data analysis

The data was summarized using mean and standard deviation as appropriate. Spearman rank correlation was used to assess the correlation between stage of ovarian cancer and NLR and PLR. The discriminative role and cut-off values of NLR and PLR were determined using receiver operating curve (ROC) analysis with Area under the Curve (AUC). The cut-off values were used to determine the sensitivity and specificity of each haematological parameter. Data analysis was done with statistical package for the social sciences (SPSS) version 25 at 95% confidence interval, with the p value set at ≤0.05 for statistical significance.

Ethical consideration

The research and ethics committee of the University of Port Harcourt Teaching Hospital granted ethical approval for the study with ethical clearance certificate number of UPTH/ADM/90/S. II/VOL.XI/1101. Prior to their inclusion in the study, participants provided written informed consent. Personal identifying information was kept confidential.

RESULTS

Fifty-seven patients were recruited into the study. Most 20 (35.1%) were aged 45-54 years, with a mean age of 46.9±11.3 years. Majority 37 (64.9%) were married, 31 (54.4%) had tertiary education, and 49 (85.9%) were still active in their respective occupation. This is shown in Table 1. The median pre-treatment NLR was 2.3 (1.7) and the median pre-treatment PLR was 126 (145) among ovarian cancer patients as shown in Table 2. Bivariate analysis using spearman correlation coefficient shows that there was a significant statistical relationship between pre-operative NLR and PLR (rho=0.758; p value <0.001) among ovarian cancer patients as shown in Table 3. This implies that an increase in NLR was strongly correlated with an increase in PLR.

Table 1: Socio-demographic profile of ovarian cancer patients (N=57).

Attributes	n (%)
Age (years)	
≤24	1 (1.8)
25-34	6 (10.5)
35-44	17 (29.8)
45-54	20 (35.1)
55-64	9 (15.8)
≥65	4 (7.0)
Marital status	
Single	11 (19.3)
Married	37(64.9)
Divorced	2 (3.5)
Widowed	7 (12.3)
Education	
None	3 (5.2)
Primary	7 (12.3)
Secondary	16 (28.1)
Tertiary	31 (54.4)
Occupation	
#Technical/associate professional	7 (12.3)
$Professional	16 (28.1)
%Clerical support	1 (1.8)
&Elementary	4 (7.0)
!Service/sales workers	11 (19.3)
Skilled workers/farmers/fishermen	4 (7.0)
<Craft/ related trade/traders	14 (12.5)
Occupation	
Active	49 (85.9)
Inactive	5 (8.8)
Retired	3 (5.3)
Median parity	3 (4)
Median no. of living children	3 (4)
Age at menarche	13 (1)

#Civil/public servant, auxiliary nurse; $doctors, engineers, lawyers, nurses, clergy; %secretaries, &housewives, students; !businessmen; >farmers/fishermen, <tailors, traders, shoemakers

Bivariate analysis using spearman correlation coefficient shows that there was significant negative statistical relationship between pre-operative NLR (rho=-0.571; p value=0.001), pre-operative PLR (rho=-0.392; p value=0.02) and elevated CA125 and CEA values among ovarian cancer patients. This illustrates that an increase in both NLR and PLR is negatively correlated with Ca125 and CEA. There was also a statistically significant positive correlation between NLR and PLR and stage of ovarian cancer (p=0.001). This implies that the higher the NLR and PLR, the more advanced the stage of ovarian cancer. This is shown in Tables 4 and 5.

Table 2: Distribution of LMR, NLR, PLR among ovarian cancer patients (N=57).

Attributes	Median (IQR)
Median LMR	4.9 (4.4)
Median NLR	2.3 (1.7)
Median PLR	126 (145)

LMR: lymphocyte to monocyte ratio, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio

Table 3: Relationship between pre-operative NLR and PLR among ovarian cancer patients.

Parameters	Rho	P value
NLR versus PLR	0.758	<0.001

*Significant at p<0.05, r: correlation coefficient

Partial correlation was used to analyze the correlation between NLR + CA125 and PLR + CA125 against staging of ovarian cancer by controlling age, age at menarche and parity as shown in Table 6. However, there was no statistically significant positive correlation between NLR + CA125 (0.019) and PLR + CA125 (0.139) with ovarian cancer staging (p>0.05).

Predictive models were performed through ROC curve analysis on NLR + Ca125 and PLR + Ca125 against stage IV of ovarian cancer as an outcome in the study. Variables with an area under the curve (AUC) greater than 0.7 were used as predictive models. NLR + Ca125 has a sensitivity value of 74.8% and specificity of 66.9% with a cut-off value of 2.6. PLR + Ca125 has a sensitivity of 59.3% and specificity of 71.6% with a cut off value of 155.8 (Table 7). None was feasible to be used as predictive model because AUC was less than 0.7 as shown in Figure 1. This means that there is less than a 70% chance of the model correctly classifying patients in this study.

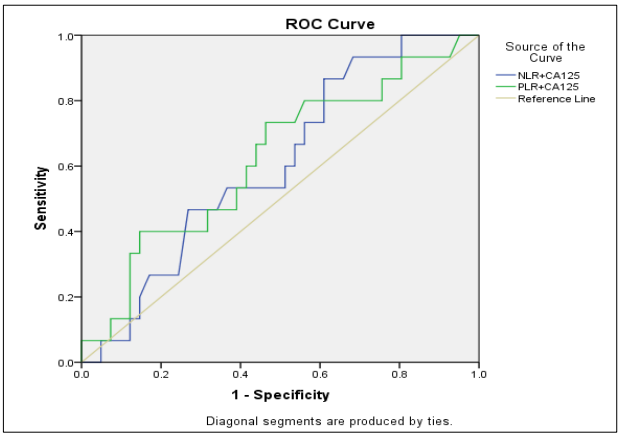

Figure 1: ROC Analysis of NLR+Ca125 and PLR+Ca125 combined as predictive value in the stage IV of ovarian cancer.

Table 4: Relationship between pre-operative NLR and pathological characteristics among ovarian cancer patients.

Parameters	Rho	P value	Median NLR	P value@
Ca125	-0.571	0.001*		
CA-199	-0.120	0.54		
CEA	-0.277	0.09		
AFP	0.432	0.16		
LDH	-0.400	0.60		
Histology				
Serous			3.18	
Mucinous			2.83	0.16
Endometroid			2.46	
Stage of cancer				
II			2.02	
III			2.78	0.001*
IV			7.44	

*Significant at p<0.05, rho: correlation coefficient; @Kruskal-Wallis test

Table 5: Relationship between pre-operative PLR and pathological characteristics among ovarian cancer patients.

Parameters	Rho	P value	Median PLR+CA125	P value@
Ca125	0.258	0.02*		
CA-199	0.074	0.72		

Continued.

Parameters	Rho	P value	Median PLR+CA125	P value@
CEA	-0.392	0.06		
AFP	0.340	0.28		
LDH	0.00	1.00		
Histology				
Serous			13.2	
Mucinous			4.98	0.43
Endometroid			12.5	
Stage of cancer				
II			10.1	
III			11.4	0.001*
IV			12.9	

*Significant at p<0.05, rho: correlation coefficient; @Kruskal-Wallis test

Table 6: Correlation between pre-operative NLR+CA125 and PLR+CA125 with stage IV of ovarian cancer after adjustment for age, age at menarche and parity.

Parameters	R	P value
NLR + Ca125	0.019	0.90
PLR + Ca125	0.139	0.36

*Statistically significant at p<0.05

Table 7: Summary of ROC analysis: AUC, cut-off point, sensitivity and specificity.

Parameters	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)	P value
NLR+Ca125	0.61	0.45-0.76	2.6	74.8	66.9	0.23
PLR+Ca125	0.62	0.46-0.79	155.8	59.3	71.6	0.16

*Significant at p<0.05; AUC: area under the curve; CI; confidence interval ; accuracy = (533+6100/2000)×100 =57.1%

DISCUSSION

One of the most widely debated topics in recent years has been the relationship between cancer and immunity. Many studies have shown that the systemic inflammatory response is important in cancer development.[29-31] Many cancers are caused by environmental factors and develop in areas that are chronically irritated and inflamed.[30] Neutrophilia, thrombocytosis, and relative lymphopenia are all indicators of systemic inflammation in the peripheral blood.[30] These immune cells and inflammatory mediators are important components of the tumour microenvironment. It is unknown how increased neutrophil and decreased lymphocyte counts cause tumour progression. Neutrophils produce a variety of inflammatory cytokines, including vascular endothelial growth factor (VEGF) and matrix metalloproteinase 9, which cause DNA damage, inhibit apoptosis, and promote angiogenesis.[30]

NLR and PLR are simple and low-cost parameters that reflect host immune response. They have been shown to be independent prognostic factors in a variety of cancers, assisting in the selection of the best treatment.[32,33] NLR and PLR have been shown to be markers of malignancy in patients with pathological ovarian masses, but the data is limited and contradictory. [34,35]

The diagnostic accuracy of pretreatment NLR and PLR in patients with ovarian cancer was investigated in our study, which revealed that high NLR and PLR was associated with advance-stage disease. Similarly, in China, researchers observed a correlation between NLR and stage, and that ovarian cancer patients with high NLR had a shorter postoperative PFS and a higher mortality rate.[36]

Furthermore, Williams reported that in 519 ovarian cancer patients, elevated NLR not only indicated a poor prognosis but also had an association with clinical-pathological features of the disease such as stage, grade, and presence of ascites.[37] Likewise, Zheng-Feng observed that elevated NLR was linked to advanced stage, CA 125 elevation, and ascites, and that it could predict the feasibility of cyto-reduction.[38]

In accordance with the sub-analysis of the result of this study, the NLRs and PLRs of patients with advanced stage (3 or 4) ovarian cancer were higher than those of patients with localized stage (1 or 2) ovarian cancer. It is thought that NLRs and PLRs increase as cancer progresses, so increases in NLRs and PLRs are associated with advanced ovarian cancer and may be associated with poor prognosis. Similar observations were made by Yun et al in Korea.[39]

Increases in NLR and PLR are not cancer-specific findings. Furthermore, an increase in these values does not indicate an absolute risk of ovarian cancer and may be transient depending on a variety of factors. CBC with differential count, on the other hand, is a common and inexpensive preoperative test. As a result, while it is not a

confirmatory test for ovarian cancer, it has clinical utility as an auxiliary tool for differential diagnosis prior to surgery. The precise diagnostic cut-off values for NLRs and PLRs for diagnosing malignant ovarian tumours have yet to be determined.

According to this study, the NLR cut-off value for malignant ovarian tumours was 2.6, while the corresponding PLR cut-off value was 155.8. These findings are consistent with previous research.[39] Regarding our findings, if the NLR is greater than 2.6 and/or the PLR is greater than 155.8, there is a greater likelihood of malignant ovarian tumours than benign or borderline tumours.

The limitation of the study was the small sample size, and the patients were not followed up on to assess overall survival. In addition, because our centre is a foremost tertiary referral hospital in Rivers State, many ovarian cancer patients seen here have advanced disease. The fact that the study is a single-centre study with patients evaluated by the same team over time is an advantage. Furthermore, future longitudinal studies regarding determination of cut-off values may also be done to determine an acceptable level of sensitivity and specificity for NLR and PLR.

CONCLUSION

The PLR and NLR could not be used as predictive markers in this study, but they may have some diagnostic value, as evidenced by previous research. However, they cannot be completely independent of other clinical, laboratory, and radiologic features indicative of malignancy at this time. Although the CBC parameters are important cost-effective tools, they may still be influenced by unaccounted variables and pathologies other than ovarian neoplasms. As a result, we recommend that NLR and PLR be evaluated further in comparison to other currently used diagnostic modalities such as CA-125, International Federation of Gynaecology and Obstetrics (FIGO) staging, and imaging studies to determine their acceptability as a predictive marker. Cut-off value studies may also be conducted to determine an acceptable level of sensitivity and specificity for NLR and PLR.

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