African Journal of Laboratory Haematology and Transfusion Science

Vol 3, Issue 1, Page 1 - 12 | March 2024 | www.ajlhtsonline.org
ARTICLE DOI: 10.59708/ajlhts.v3i1.2328
DOI URL: doi.org/10.59708/ajlhts.v3i1.2328

ORIGINAL ARTICLE

High pre-and post-treatment Platelet-Neutrophil to Lymphocyte ratio is linked to high mortality risk in Epithelial Ovarian Cancer patients in South-eastern Nigeria

Jude Ogechukwu Okoye,[1*] Tochukwu Juliet Ado-Okoye, [1]Chiemeka Michael Emeka, [2]George Uchenna Eleje,[3] Immaculata Ogochukwu Uduchi,[1] Uchechukwu Lilian Okoye[4]

[1]Department of Medical Laboratory Science Department, Nnamdi Azikiwe University, Nnewi, Nigeria.

[2]Department of Anatomic Pathology and Forensic Medicine, Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria.

[3]Department of Gynaecology, Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria.

[4]Department of Pharmacy, Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria.

*Corresponding Author: jog.okoye@unizik.edu.ng

JOO: jog.okoye@unizik.edu.ng
TJA: tochukwuujulieth@gmail.com
CME: me.onwukamuche@unizik.edu.ng
GUE: georgel21@yahoo.

Abstract

Introduction: To identify risk factors and prognostic tools for epithelial ovarian cancer (EOC), an aggressive ovarian cancer, this study assessed the frequency of BRCA2 mutation in early-onset (≤ 50 years old) and late-onset (> 50 years old) EOC and variation of systemic immune-inflammatory indices, especially among herbal medicine- and chemotherapy-experienced patients.

Methods: This study included 100 patients diagnosed with EOC from Jan. 2016 to Dec. 2021. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), platelets-neutrophils-to-lymphocytes ratio (PNLR), and neutrophils-to-lymphocytes platelets ratio (NLPR) were assessed and analyzed accordingly. Significance was set at $p< 0.05$.

Result: The frequency of early menarche, serous adenocarcinoma, in-hospital death, and late-stage disease was 3.3, 1.6, 1.7, and 1.4 times higher among patients with early-onset EOC compared with their late-onset counterparts ($p= 0.001$, 0.025, 0.063, and 0.397, respectively). The frequency of BRCA2 mutation, hypertension, and diabetes was 2.5, 2.5, and 5.7 times higher among the latter than among the former ($p= 0.001$, 0.006, and 0.064, respectively). The pre-/post-treatment PNLR were 1.7/2.3 times significantly higher in cases of in-hospital death (1016.0 ± 169.4/ 750.5 ± 193.2) than in patients who were stable on discharge (591.60 ± 25.3/325.3 ± 35.3 at $p= 0.044$ and 0.013, respectively. There was a significant decline of pre-to-post-chemotherapy PNLR in the Stages I/II cases and an insignificant decline in Stages III/IV cases ($p= 0.003$ and 0.433, respectively). The post-treatment PNLR, PLR, and TWBC of herbal medicine-experienced patients were 5.6, 1.6, and 1.5, higher than the post-treatment values of naïve counterparts, respectively ($p< 0.05$).

com
IOU: io.uduchi@unizik.edu.ng
ULO: ul.okoye@unizik.edu.ng

Received: 15-08-2023
Accepted: 09-02-2004
Published: 30-03-2004

Conclusion: This study revealed a high frequency of aggressive early-onset EOC and a higher frequency of BRCA2 mutation in late-onset EOC. It also revealed better treatment outcomes among patients who received at least four courses of chemotherapy and poor treatment outcomes among patients with a history of herbal medicine uptake. It suggests that NLR, PNLR, and PLR could be used to monitor disease progression.

Keywords: Immune cells, Inflammation, prognosis, disease stage

Introduction

Ovarian cancer is the third most common cancer among females in West Africa (1). Evidence shows a higher mortality rate among women of African descent (2). On average, there is a 2.1% annual increase in the countries within the West African region from 1995 to 2019 (3). About 75% of ovarian cancer patients are diagnosed with late-stage disease (4,5), with a poor prognosis and a high risk of reoccurrence (6). As of 2020, reports show that the pool prevalence of EOC among other ovarian tumours in Southern Nigeria was 72.4% (7). Patients with EOC have a shorter disease-free survival period (8). Evidence shows that each five-year increase in age at menopause is associated with a 6% increase in ovarian cancer risk (9), possibly due to the increased risk of BRCA2 mutation, especially among patients who are older than 50 years (10,11) Such BRCA-mutated ovarian cancers exhibit significantly higher inflammatory burden than BRCA wild type (12). Patients living in countries with low/medium human development index bear the cost of cancer management. As a result, clinicians are searching for affordable prognostic systemic biomarkers to identify women with poor prognoses and assess chemotherapy response (13). Systemic inflammation is linked to cancer initiation, progression, and metastasis (14); it has been related to cancer mortality (15) and is employed as a useful prognostic indicator in many solid tumours (16). Neutrophilia, an inflammatory process, promotes angiogenesis and immune suppression (17) while pre-treatment thrombocytosis favours advanced disease stage and high-grade epithelial ovarian cancer (7). To improve the predictive potential of inflammatory markers, scientists are currently assessing the ratio of one immune cell to another. Studies have shown that neutrophil-to-lymphocyte (NLR), platelet-to-lymphocyte ratio (PLR), and platelets-neutrophils to lymphocytes ratio (PNLR) could be used as prognostic biomarkers based on their potential to predict poor overall survival and unfavourable progression-free survival (18,19), and tumours stage (20,21). To identify prognostic tools and disease confounders of EOC, this study assessed the frequency of BRCA2 mutation, demographic characteristics, and SIII variation as determinants of early-onset (≤ 50 years) EOC and treatment outcomes. To the best of our knowledge, this is the first study to assess BRCA2 mutation and the prognostic systemic immuno-inflammatory indices (SIII) in early-onset (≤ 50 years) and late-onset (> 50 years) EOC in West Africa.

Methods

Study Population and Ethics

In this retrospective study, a total of 105 patients with epithelial ovarian cancer (EOC) cases, diagnosed from January 2017 to December 2021 in Nnamdi Azikiwe University Teaching Hospital (NAUTH), and some private clinics in Nnewi and Onitsha were identified. Patients with inadequate records, especially clinical and haematological data (n = 3) and mixed tumours (n = 2) were excluded from the study. Finally, a total of 100 patients diagnosed with epithelial ovarian cancer were included in this study. Patients received carboplatin and paclitaxel as platinum chemotherapy intravascularly every two weeks apart. The chemotherapy dose was calculated using the formula = Body surface area-based dose x square root [Height (cm) x Weight (kg)/3600]. This retrospective study was approved by the NAUTH ethics committee (NAUTH/CS/66/VOL.14/VER.3/35/2021/07). The patient's medical records were accessed for socio-clinical demographics such as age, gender, comorbidities, and time of presentation. All analyses were performed by the ethical standards laid down in the Declaration of Helsinki; all investigations were carried out with utmost consideration for patient confidentiality and safety.

Sample collection and handling

Venous blood samples were taken on patients' admission (5 ml; pre-treatment sample). Blood samples were also taken a week before the first chemotherapy (5 ml; pre-chemotherapy sample) and a week after chemotherapy (5 ml; post-chemotherapy). All blood samples were collected into EDTA bottles. Full blood counts were carried out on the whole blood samples using a Haemo-autoanalyzer. At the time of admission, cases of ovarian cancer were confirmed based on transvaginal ultrasound (TVU), CA-125 levels and biopsy results. Following ultrasound investigations, biopsy, and surgery, resected tissues were sent to the Department of Morbid Anatomy and Forensic Medicine for histological investigation. Retrospectively, sections of the viable archived tissue blocks were cut and stained by the Haematoxylin and Eosin (H&E) staining technique. Two pathologists evaluated the tissues for evidence of malignancy based on the International Federation of Obstetrics and Gynecology (FIGO) guidelines. The total white cell count (TWBC) ($10^{\wedge 9}$/L), NLR, PLR, PNLR (Platelet count x Neutrophil count]/Lymphocyte count), and neutrophils-to-lymphocytes-platelets ratio (NLPR; [Neutrophil count x 100]/Lymphocyte count x platelet count]) were calculated for the subgroups.

Procedure for Immunohistochemistry:

Following ethical approval, the H&E-stained tissue sections were reviewed and investigated for BRCA2 expression. During immunohistochemistry, the sections from EOCs were first dewaxed and hydrated. The Epitopes in sections were then retrieved. Sections were treated with peroxidase blocker and subsequently washed in phosphate Buffered Saline (PBS). The sections were treated with the primary antibody (BReast CAncer gene 2; BRCA2) for 60 minutes in a humidity chamber, washed in PBS, and treated with the secondary antibody accordingly. The slides were then washed in PBS for 2 minutes. The sections were treated with Horseradish peroxidase and washed in 2 changes of PBS. The sections were stained with 3,3′-Diaminobenzidine (1 drop in 1 ml of Substrate), washed in PBS, stained with Haematoxylin, washed in PBS, and distilled water, dehydrated, cleared, and mounted with a DPX. The Sections were then scored based on staining intensity (0, 1, 2, and 3). Scores 0 and 1 were considered negative (mutation).

Statistical analysis

Chi-square/Fisher was used to determine the association between the socio-clinical demographics of patients 50 years and those > 50. Pearson's correlation was used to determine the relationship between the SIII before and after the last treatment. T-test was used for comparing data of 1. patients aged ≤ 50 years and > 50 years, 2. chemotherapy naïve and experienced patients, 3. patients who received 1-3 cycles and 4-6 cycles of chemotherapy, 4. herbal medicine-experienced (Patients who consumed herbal medicine for their ailment before presentation at NAUTH) and naïve patients, and 5. patients with and without metastatic tumours. ANOVA was used to compare data of patients who presented at ≤

6 months and > 6 months, and patients who were stable, unstable, and dead at discharge (in-hospital death).

Results

In this study, the prevalence of EOC among other malignant tumours was 81.1%. The mean and median ages and age range of the patients diagnosed with ovarian cancer were 55.64 ± 13.75 years, 56.0 years, and 15 to 82 years, respectively. The reduced number of diagnoses observed in the year 2019 could be due to the limited healthcare services offered during the COVID-19 pandemic (figure 1).

Age-based socio-clinical differences

Even though the level of tertiary education was 2.7 times higher among patients ≤ 50 years old compared with their over 50 years counterparts at ($p< 0.05$), the unemployment rate was 3.6 times higher among the former compared with the latter at $p< 0.05$ (table 1). The lower employment rate among the patients aged ≤ 50 years may explain why they had a lower uptake of chemotherapy compared with their over 50 years old counterparts ($p> 0.05$). Although a higher percentage of the patients aged ≤ 50 years presented at the clinic within six months of symptoms manifestation compared with over 50 years counterparts ($p< 0.05$), the rate of in-hospital death was higher among patients aged ≤ 50 years (14/26%; 53.8%) compared with their over 50 years old counterparts (24/74; 32.4%) at $p= 0.199$.

The median and mean survival rates were also lower among patients ≤ 50 years old (102 and 195.5 ± 67.15 years) compared with their over 50 years old counterparts (188 and 324.9 ± 71.7 years) at $p= 0.317$. Even though BRCA2 loss because of mutation (figure 2) was 2.2 times lower among patients aged ≤ 50 years compared with their over 50 years counterparts ($p< 0.05$), the frequency of late-stage disease (stage III and IV) and serous adenocarcinoma was 1.4 and 1.6 times higher among the former than the latter at $p> 0.05$ and $p< 0.05$, respectively. The rate of early menarche (12 and 13 years) was 3.3 times higher among patients ≤ 50 years old compared with their over 50 years counterparts ($p< 0.05$). The frequency of hypertension was 2.5 times lower among patients aged ≤ 50 years compared with their over 50 years counterparts ($p< 0.05$). A higher frequency of in-hospital death was observed among patients with early-onset EOC (≤ 50 years) compared with late-onset EOC (> 50 years) at $p> 0.05$.

Comparison of chemotherapy and herbal medicine outcomes

The post-treatment TWBC and PNLR were 1.6 and 1.5 times lower among chemotherapy-experienced patients compared with chemotherapy naïve patients at $p< 0.05$ and $p> 0.05$, respectively. The post-treatment PNLR, NLPR, TWBC, NLR, and PLR of the patients who received more than three courses of chemotherapy were 2.7, 2.5, 1.9, 1.7, and 1.4 times lower than the values recorded among patients who received three or fewer courses of chemotherapy at $p> 0.05$, $p> 0.05$, $p< 0.05$, $p> 0.05$, and $p> 0.05$, respectively. The pre-treatment PLR, PNLR, NLPR, and NLR of herbal medicine-experienced patients were 1.9, 1.7, 1.4, and 1.1 times lower compared with the pre-treatment values of their naïve counterparts at $p< 0.05$, $p> 0.05$, $p>0.05$, and $p> 0.05$, respectively. The post-treatment PNLR, PLR, TWBC, NLR, and NLPR of herbal medicine-experienced patients were 5.6, 1.6, 1.5, 1.3, and 1.2 times higher compared with the post-treatment values of their naïve counterparts at $p< 0.05$, $p< 0.05$, $p< 0.05$, $p> 0.05$, and $p> 0.05$, respectively.

The pre-treatment-to-post-treatment NLPR of both herbal medicine-experienced and naïve patients significantly increased by 5.4 and 3.4 times, respectively ($p< 0.05$). Of note, the median survival rate of herbal medicine-experienced and naïve patients was 86 days and 202 days, respectively, and only 50% (n = 10) of herbal medicine-experienced patients were also chemotherapy-experienced. Thus, it could be inferred that though patients with a history of herbal medicine had a lower pre-treatment SIII, they had poor treatment outcomes compared with their herbal medicine-naïve participants. Although the pre-treatment PNLR was 2.1 times higher among patients with stages I and II ovarian cancer compared with patients with stages III and IV ovarian cancer ($p< 0.05$), there was a 2.5 times significant decline and 1.1 times insignificant decline in the pre-to-post-treatment PNLR among the former and the latter at $p< 0.05$ and $p> 0.05$, respectively (table 2).

In Table 3, the pre-/post-treatment NLR and PNLR were 2.2/2.4 and 1.7/2.3 times higher in cases of in-hospital death than among patients who were stable on discharge ($p< 0.05$).

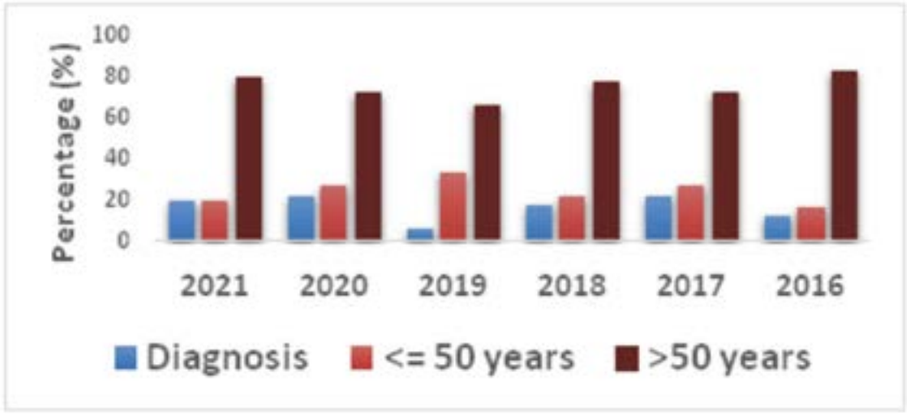

Figure 1: Trend of ovarian cancer cases per year

Figure 1 shows that the rate of diagnosis per year was relatively the same from 2016 through 2021, except in 2019 where there was a decline in the number of cases. In 2019, the number of early-onset (≤ 50 years) cases was higher than in other years.

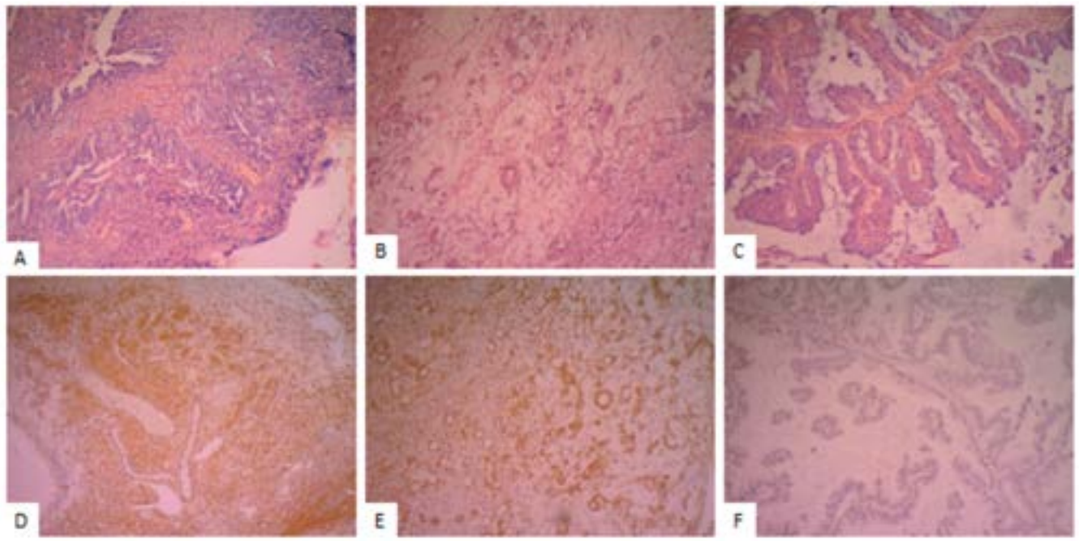

Figure 2: Sections of invasive ovarian cancer

In Figure 2, sections A to C were H&E stained while sections D to F were stained by the immunohistochemical technique (magnification= X200). Sections D and E are positive for BRCA2 protein while section F is negative for BRCA2 protein. Of note, A/D, B/E, and C/F are corresponding sections.

Table 1: Socio-clinical characteristics of patients diagnosed with ovarian cancer

Variables	Total	≤ 50 years	>50 years	p- value
	N= 100	n= 26 (%)	n= 74 (%)	
Employment status:				0.002*
Civil servant	24	2 (7.7)	22 (29.7)	
Unemployed/Dependant	18	10 (38.5)	8 (10.8)	
Self-employed	58	14 (53.8)	44 (59.5)	
Level of Education:				<0.001*
No formal education	9	1 (3.8)	8 (10.8)	
Basic education	52	6 (23.1)	46 (62.2)	
Tertiary education	39	19 (73.1)	20 (27.0)	
Alcohol consumption:				0.144
No	82	24 (92.3)	58 (78.4)	
Yes	18	2 (7.7)	16 (21.6)	
Tobacco Use:				0.280
No	89	25 (96.2)	64 (86.5)	
Yes	11	1 (3.8)	10 (13.5)	
History of Hypertension:				0.006*
No	52	20 (76.9)	32 (43.2)	
Yes	48	6 (23.1)	42 (56.8)	
Diabetes Mellitus				0.064
No	83	25 (96.2)	58 (78.4)	
Yes	17	1 (3.8)	16 (21.6)	
History of Herbal medicine:				0.776
No	80	20 (76.9)	60 (81.1)	
Yes	20	6 (23.1)	14 (18.9)	
History of fertility drug uptake:				0.726
No	88	24 (92.3)	64 (86.5)	
Yes	12	2 (7.7)	10 (13.5)	
Menarche:				0.001*
12-13 years	26	14 (53.8)	12 (16.2)	
14-15 years	63	11 (42.3)	52 (70.3)	
≥16 years	11	1 (3.9)	10 (13.5)	
Parity:				0.474
0	30	10 (38.5)	20 (46.2)	
≤ 2	14	4 (15.4)	10 (13.5)	
≥ 3	56	12 (46.1)	44 (59.5)	
TSMP:				0.009*
≤ 6 months	62	22 (84.6)	40 (54.1)	
> 6 months	38	4 (15.4)	34 (45.9)	
Histologic type:				0.025*
Serous	64	23 (88.5)	41 (55.4)	
Endometrioid	21	2 (7.7)	19 (25.7)	
Mucinous	10	1 (3.9)	9 (12.2)	
Clear-cell	5	0 (0.0)	5 (6.7)	
FIGO Staging:				0.397
Stage 1	24	4 (15.4)	20 (27.0)	
Stage 2	28	6 (23.1)	22 (29.7)	
Stage 3	14	4 (15.4)	10 (13.5)	
Stage 4	34	12 (46.1)	22 (29.7)	
BRCA2 expression				0.001*
Negative	56	7 (26.9)	49 (66.2)	
Positive	44	19 (73.1)	25 (33.8)	
Chemotherapy experience:				0.165
No	41	14 (53.8)	27 (36.5)	

Yes	59	12 (46.2)	47 (63.5)	
In-Hospital Death				
No	62	12 (46.2)	50 (67.6)	0.063
Yes	38	14 (53.8)	24 (32.4)	

TSMP: Time of symptom manifestation to presentation. Descriptive analysis and Chi-square/Fisher's exact test. *Significance was set at p < 0.05.

Table 2: Comparative analysis of haematological indices based on chemo/herbal therapy experience and metastasis.

Parameters	Chemotherapy		p-value	Courses of Chemotherapy		p-value
	Naive	Experienced		1 to 3 courses	4 to 6 courses	
	n= 41	n= 59		n= 18	n= 41	
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Pre-TWBC (10^9/L)	9.29 ± 1.79	6.46 ± 0.70	0.098	6.14 ± 0.46	5.62 ± 0.43	0.443
Post-TWBC (10^9/L)	8.30 ± 2.10	5.10 ± 0.54	0.040*	8.04 ± 1.48	4.21 ± 0.40	0.003*
P- value	0.787	0.148		0.166	0.026*	
Pre-NLR	3.58 ± 0.82	2.71 ± 0.58	0.375	1.79 ± 0.21	1.86 ± 0.38	0.886
Post-NLR	1.72 ± 0.37	1.99 ± 0.42	0.774	2.11 ± 0.56	1.26 ± 0.16	0.059
P- value	0.253	0.343		0.514	0.182	
Pre-PLR	266.4 ± 63.06	209.0 ± 24.31	0.347	152.0 ± 11.95	244.9 ± 28.67	0.042*
Post-PLR	168.2 ± 40.56	161.7 ± 21.94	0.899	178.1 ± 62.78	129.7 ±14.32	0.269
P- value	0.423	0.159		0.628	0.002*	
Pre-PNLR	1144 ± 407.9	880.9 ± 245.8	0.573	454.4 ± 67.15	525.8 ± 78.99	0.523
Post-PNLR	718.6 ± 306.5	473.1 ± 126.7	0.424	929.7 ± 515.3	343.2 ± 52.04	0.108
P- value	0.492	0.143		0.339	0.060	
Pre-NLPR	0.19 ± 0.06	0.15 ± 0.03	0.543	0.11 ± 0.03	0.12 ± 0.03	0.868
Post-NLPR	0.52 ± 0.14	0.99 ± 0.19	0.263	1.74 ± 0.59	0.71 ± 0.14	0.039*
P- value	0.020*	< 0.001*		0.008*	<0.001*	

Parameters	Herbal medicine			FIGO Stages		p-value
	Naive	Experienced		Stages I & II	Stages III & IV	
	n= 79	n= 21	p- value	n= 52	n= 48	
Pre-TWBC (10^9/L)	5.63 ± 0.35	5.88 ± 0.88	0.728	5.60 ± 0.35	5.41 ± 0.38	0.743
Post-TWBC (10^9/L)	4.54 ± 0.32	7.18 ± 1.59	0.013*	4.68 ± 0.61	5.08 ± 0.48	0.641
P- value	0.037*	0.358		0.169	0.586	
Pre-NLR	1.70 ± 0.18	1.55 ± 0.28	0.669	2.03 ± 0.27	2.37 ± 0.51	0.526
Post-NLR	1.46 ± 0.17	1.97 ± 0.51	0.267	1.31 ± 0.19	1.85 ± 0.25	0.098
P- value	0.344	0.454		0.072	0.380	
Pre-PLR	236.7 ± 22.38	127.5 ± 14.40	0.010*	209.0 ± 24.33	190.9 ± 27.54	0.646
Post-PLR	140.5 ± 15.08	222.5 ± 46.32	0.039*	161.5 ± 28.55	165.0 ± 23.30	0.928
P- value	0.002*	0.030*		0.218	0.490	
Pre-PNLR	744.1 ± 107.1	431.0 ± 76.52	0.178	843.1 ± 130.1	410.5 ± 40.26	0.031*
Post-PNLR	348.8 ± 42.60	1950.0 ± 541.8	<0.001*	326.2 ± 50.76	369.2 ± 32.61	0.518
P- value	0.001*	0.010*		0.003*	0.433	
Pre-NLPR	0.15 ± 0.02	0.11 ± 0.03	0.303	0.18 ± 0.04	0.14 ± 0.03	0.504
Post-NLPR	0.51 ± 0.07	0.59 ± 0.16	0.598	0.61 ± 0.10	0.70 ± 0.13	0.232
P- value	< 0.001*	0.001*		< 0.001*	< 0.001*	

Statistics: T-test. *Significance was set at p< 0.05.

Table 3: Comparative analysis of haematological indices based on time of symptom development to presentation and condition of the patient on discharge.

Parameters	Stable OD	In-Hospital death	p-value
	n= 42	n= 38	
	Mean ± SD	Mean ± SD	
Pre-TWBC (10^9/L)	5.75 ± 0.79	6.23 ± 0.68	0.551
Post-TWBC (10^9/L)	4.88 ± 0.84	5.96 ± 0.95	0.272
P- value	0.191	0.826	
Pre-NLR	1.61 ± 0.24	3.47 ± 0.66	0.007*
Post-NLR	1.17 ± 0.16	2.79 ± 0.28	<0.001*
P- value	0.179	0.485	
Pre-PLR	166.2 ± 22.08	297.10 ± 62.99	0.059
Post-PLR	142.2 ± 19.18	202.60 ± 45.89	0.164
P- value	0.420	0.343	
Pre-PNLR	591.6 ± 25.30	1016.0 ± 169.40	0.044*
Post-PNLR	325.3 ± 35.28	750.5 ± 193.20	0.013*
P- value	0.044*	0.316	
Pre-NLPR	0.12 ± 0.02	0.18 ± 0.04	0.166
Post-NLPR	0.72 ± 0.20	1.40 ± 0.31	0.070
P- value	0.004*	< 0.001*	

Keys: OD; On discharge. Statistics: T-test and ANOVA. *Significance was set at p < 0.05.

Discussion

This study compared the clinical features of early-onset (≤ 50 years) and late-onset (> 50 years) EOC. It also assessed the ratio of immune cells in different timelines of disease presentation and stages, and treatment history and outcomes. The frequency of late-onset ovarian cancer in this study was 2.8 times higher than the frequency of early-onset EOC. The high mean and median ages within our cohort agree with earlier studies' reports showing that older age and BRCA mutation increases the risk of developing ovarian cancer (9-11). Late-onset EOC in this study is higher than in cases diagnosed from 2000 to 2013 (32.4% to 40%) in other parts of West Africa (22-24). The reason for the variation is unknown but it could be associated timeline of diagnosis. This is underscored by the findings of Okunade et al. who earlier recorded a low frequency of late-onset EOC in western Nigeria between 2008 and 2012 (40%) and reported a higher frequency of 62% between 2010 and 2018 in the same city (25,26). The high frequency of late-onset EOC may be due to the high frequency of diabetes mellitus within the group [27]. Although most of the patients with early-onset EOC had lower frequencies of BRCA2 mutation, tobacco, alcohol, and fertility drug use, they had a higher frequency of late-stage disease compared to patients with late-onset EOC. The aggressiveness of EOC among patients with early-onset type, evidenced by a low survival rate, could be attributed to early menarche and a high frequency of serous adenocarcinoma within the group (28,29).

In this study, the prevalence of herbal medicine use is high but lower than the prevalence (28.3% to 73.8%) reported in other parts of West Africa (30). Due to the high cost of orthodox treatment in countries with low healthcare resources, patients resort to herbal products. Although positive results have been recorded in vitro studies that evaluated the anti-ovarian cancer properties of some herbal products (31,32), controversies regarding the in vivo health benefits of herbal therapies abound, especially in Africa. Studies have shown that medicinal plants contain pesticides, radioelements, microorganisms, and heavy metals such as Lead, arsenic, mercury, Cadmium, Chromium, Nickel, and Zinc (33). Apart from the potential to induce anaemia, diarrhoea, vomiting, and electrolyte imbalance, some herbal products are believed to inhibit enzymes, especially CPY isoforms, involved in drug metabolism, resulting in increased levels and toxicity (34). Li et al. reported high NLR and PLR were significantly associated with decreased OS and DFS (35). This could be the explanation for the higher post-treatment TWBC and SIII and lower median survival rate among herbal medicine-experienced patients compared with their herbal medicine-naïve counterparts and chemotherapy-experienced patients. Interestingly, patients with early-onset EOC had a higher history of herbal medicine consumption than patients with late-onset EOC. It could be argued that the consumption of herbal medicine may have contributed to the aggressiveness of the disease in patients with early-onset EOC. One of the limitations of this study was the low uptake of the full (6) course of chemotherapy. This led to a small sample subgroup size. This could be the reason for the insignificant differences in SIII values observed in this study. The contents of herbal medicine used by the patients in this study were not assessed might constitute a limitation. However, we believe that studies such as ours could be the catalyst for future robust studies.

Conclusion

This study unveils compelling findings regarding patients diagnosed with EOC in Southeastern Nigeria. It reveals a high frequency of late-onset EOC and a high frequency of in-hospital death among patients with EOC. It suggests that age at menarche and histologic type drive the aggressiveness of early-onset EOC and determine treatment outcome. It also reveals that uptake of a complete course of chemotherapy results in better treatment outcomes. Among the SIIIs, NLR, and PNLR are of better prognostic value and could be used as alternative tools for predicting treatment outcomes.

References

1. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, Bray F. Cancer statistics for the year 2020: An overview. Int J cancer. 2021;149(4):778-89.
2. Chornokur G, Amankwah EK, Schildkraut JM, Phelan CM. Global ovarian cancer health disparities. Gynecol Oncol. 2013;129(1):258-64.
3. Gizaw M, Parkin DM, Stöter O, Korir A, Kamate B, Liu B, Bojang L, N'Da G, Manraj SS, Bukirwa P, Chokunonga E. Trends in the incidence of ovarian cancer in sub-Saharan Africa. Intl J Cancer. 2023; 152(7):1328-36.
4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries: Global cancer statistics. CA Cancer J Clin. 2018;68(6):394-424.
5. Torre LA, Trabert B, DeSantis CE, Miller KD, Samimi G, Runowicz CD, Gaudet MM, Jemal A, Siegel RL. Ovarian cancer statistics, 2018. CA: a cancer J Clin. 2018; 68(4):284-96.
6. Hirose S, Tanabe H, Nagayoshi Y, Hirata Y, Narui C, Ochiai K, Isonishi S, Takano H, Okamoto A. Retrospective analysis of sites of recurrence in stage I epithelial ovarian cancer. Journal of Gynecol Oncol. 2018;29(3).
7. Zayyan MS, Ahmed SA, Oguntayo AO, Kolawole AO, Olasinde TA. Epidemiology of ovarian cancers in Zaria, Northern Nigeria: a 10-year study. Int J Women's Health. 2020;22:855-60.
8. Allensworth SK, Langstraat CL, Martin JR, Lemens MA, McGree ME, Weaver AL, Dowdy SC, Podratz KC, Bakkum-Gamez JN. Evaluating the prognostic significance of preoperative thrombocytosis in epithelial ovarian cancer. Gynecol Oncol. 2013;130(3):499-504.
9. Webb PM, Jordan SJ. Epidemiology of epithelial ovarian cancer. Best Prac Res Clin Obstet gynaecol 2017;41:3-14.
10. Kotsopoulos J, Gronwald J, Karlan B, Rosen B, Huzarski T, Moller P, Lynch HT, Singer CF, Senter L, Neuhausen SL, Tung N. Age-specific ovarian cancer risks among women with a BRCA1 or BRCA2 mutation. Gynecologic oncology. 2018;150(1):85-91.
11. Bizzarri N, D'Indinosante M, Marchetti C, Tudisco R, Turchiano F, Scambia G, Fagotti A. The prognostic role of systemic inflammatory markers in apparent early-stage ovarian cancer. Int J Clin Oncol. 2023;28(2):314-20.
12. Marchetti C, D'Indinosante M, Bottoni C, Di Ilio C, Di Berardino S, Costantini B, Minucci A, Vertechy L, Scambia G, Fagotti A. NLR and BRCA mutational status in patients with high grade serous advanced ovarian cancer. Sci Rep. 2021;11(1):11125.
13. Huang J, Hu W, Sood AK. Prognostic biomarkers in ovarian cancer. Cancer Biomarkers. 2011; 8(4-5):231-51.
14. Muinao T, Deka Boruah HP, Pal M. Diagnostic and Prognostic Biomarkers in ovarian cancer and the potential roles of cancer stem cells—an updated review. Exp Cell Res 362(1):1–10.
15. Grivennikov SI, Greten FR, Karin M (2010) Immunity, inflamma- tion, and cancer. Cell 140(6):883–899. https://doi.org/10.1016/j.cell.2010.01.025
16. Proctor MJ, McMillan DC, Horgan PG, Fletcher CD, Talwar D, Morrison DS. Systemic inflammation predicts all-cause mortality: a Glasgow inflammation outcome study. PloS one. 2015;10(3):e0116206.
17. Templeton AJ, McNamara MG, Šeruga B, et al (2014) Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis.
18. Templeton AJ, McNamara MG. B. eruga, FE Vera-Badillo, P. Aneja, A. Ocaa, R. Leibowitz-Amit, G. Sonpavde, JJ Knox, B. Tran, IF Tannock, and E. Amir,"Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: A systematic review and meta-analysis," J Natl Cancer Inst 106(6):dju124.
19. Dumitru CA, Lang S, Brandau S. Modulation of neutrophil granulocytes in the tumor microenvironment: Mechanisms and consequences for tumor progression Semin Cancer Biol. 2013;23:141–8
20. Zhu Y, Zhou S, Liu Y, Zhai L, Sun X. Prognostic value of systemic inflammatory markers in ovarian Cancer: a PRISMA-compliant meta-analysis and systematic review. BMC cancer. 2018; 18(1):1-0.
21. El Bairi K, Al Jarroudi O, Afqir S. Inexpensive systemic inflammatory biomarkers in ovarian Cancer: an umbrella

systematic review of 17 prognostic meta-analyses. Frontiers Oncol. 2021;11:694821.
22. Huang H, Wu K, Chen L, Lin X. Study on the application of systemic inflammation response index and platelet–lymphocyte ratio in ovarian malignant tumors. Intl J General Med. 2021:10015-22.
23. Mleko M, Pluta E, Pitynski K, Bodzek M, Kałamacki A, Kiprian D, Banas T. Trends in Systemic Inflammatory Reaction (SIR) during Paclitaxel and Carboplatin Chemotherapy in Women Suffering from Epithelial Ovarian Cancer. Cancers. 2023;15(14):3607.
24. Iyoke CA, Ugwu GO, Ezugwu EC, Onah N, Ugwu O, Okafor O. Incidence, pattern and management of ovarian cancer at a tertiary medical center in Enugu, Southeast Nigeria. Ann Med Health Sci Res. 2013 Sep 18;3(3):417-21.
25. Okunade KS, Okunola H, Okunowo AA, Anorlu RI. A five-year review of ovarian cancer at a tertiary institution in Lagos, South West, Nigeria. Accessed on 18/07/23. Available at https://ir.unilag.edu.ng/handle/123456789/10071
26. Okunade KS, Adejimi AA, Ohazurike EO, Salako O, Osunwusi B, Adenekan MA, Ugwu AO, Soibi-Harry A, Dawodu O, Okunowo AA, Anorlu RI. Predictors of survival outcomes after primary treatment of epithelial ovarian cancer in Lagos, Nigeria. JCO Global Oncol. 2021;7:89-98.
27. Lee JY, Jeon I, Kim JW, Song YS, Yoon JM, Park SM. Diabetes mellitus and ovarian cancer risk: a systematic review and meta-analysis of observational studies. Int J Gynecol Cancer. 2013;23(3).
28. Gong TT, Wu QJ, Vogtmann E, Lin B, Wang YL. Age at menarche and risk of ovarian cancer: a meta-analysis of epidemiological studies. Int J cancer. 2013;132(12):2894-900.
29. Alegbeleye BJ, Akpoveso OO, Mohammed RK. The use of herbal medicines by cancer patients in contemporary African settings: a scoping review. Int J Sci Adv. 2020;1:49-73.
30. Zhu K, Fukasawa I, Furuno M, Inaba F, Yamazaki T, Kamemori T, Kousaka N, Ota Y, Hayashi M, Maehama T, Inaba N. Inhibitory effects of herbal drugs on the growth of human ovarian cancer cell lines through the induction of apoptosis. Gynecol Oncol; 97(2):405-9.
31. Ben-Arye E, Lavie O, Samuels N, Khamaisie H, Schiff E, Raz OG, Mahajna J. Safety of herbal medicine use during chemotherapy in patients with ovarian cancer: a "bedside-to-bench" approach. Med Oncol. 2017 Apr;34:1-6.
32. Awodele O, Popoola TD, Amadi KC, Coker HA, Akintonwa A. Traditional medicinal plants in Nigeria—Remedies or risks. J Ethnopharmacol. 2013; 150(2):614-8.
33. Mrozek-Szetela A, Rejda P, Wińska K. A review of hygienization methods of herbal raw materials. Appl Sci. 2020;10(22):8268.
34. Başaran N, Paslı D, Başaran AA. Unpredictable adverse effects of herbal products. Food Chem Toxicol. 2022;159:112762.
35. Li Y, Jia H, Yu W, Xu Y, Li X, Li Q, Cai S. Nomograms for predicting the prognostic value of inflammatory biomarkers in colorectal cancer patients after radical resection. Intl J Cancer. 2016; 139(1):220-31.

How to cite this article:

Okoye JO, Ado-Okoye TJ, Emeka CM, Eleje GU, Uduchi IO, Okoye UL. High pre-and post-treatment Platelet-Neutrophil to Lymphocyte ratio is linked to high mortality risk in Epithelial Ovarian Cancer patients in Southeastern Nigeria. *Afr J Lab Haem Transf Sci* 2024;3(1): 1- 12. **DOI:** https://doi.org/10.59708/ajlhts.v3i1.2328